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NAME OF SUPERVISOR/NOM DU DIRECTEUR DE THÈSE DR. J. C. Russell

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THE UNIVERSITY OF ALBERTA

URINE PRODUCTION IN THE AWAKE AND HALOTHANE-
ANESTHETIZED RABBIT

by



BRYANT F. LITCHFIELD

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
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DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and
recommend to the Faculty of Graduate Studies and Research,
for acceptance, a thesis entitled URINE PRODUCTION IN
..... THE AWAKE AND HALOTHANE-ANESTHETIZED RABBIT
.....
submitted by BRYANT FLOYD LITCHFIELD
.....
in partial fulfilment of the requirements for the degree of
Master of Science in EXPERIMENTAL SURGERY.

.....
Supervisor

.....

.....

Date August 31, 1978

DEDICATION

To Dianne and Becki Jo Litchfield

ABSTRACT

Urine and blood parameters were studied in three groups of rabbits; fed controls, fasted, and animals subjected to anesthesia and abdominal surgery. Water was freely available to the fed or fasted animals. During anesthesia and operation, animals were given no intravenous fluid, or saline according to one of three infusion rates (0.5 ml, 1.0 ml, or 2.0 ml per minute).

The results demonstrate that an intravenous saline infusion of 0.5 ml per minute is beneficial to unstressed rabbits during anesthesia and surgery. However, with such an infusion, the rabbits essentially do not produce urine under the experimental conditions. Higher rates of infusion are associated with a declining heart rate and blood pressure, abnormal urine, and metabolic acidosis. We conclude that the rabbit is an inappropriate species for renal studies involving anesthesia with halothane, and surgery.

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CHAPTER I

INTRODUCTION

Life, at the cellular level, is dependent on the constancy of the internal environment of the body. One of the major organs responsible for maintaining this constancy, is the kidney. It eliminates toxic wastes, and maintains water, acid-base, and electrolyte balances by elimination or retention depending on the status of the internal environment. Together, the kidneys receive almost a quarter of the cardiac output: an extremely high blood flow per unit weight. The renal role in maintaining the internal environment is accomplished, in part, by ultrafiltration of about one fifth of the plasma flow. Much of the water and solutes (glucose, for example) is then selectively reabsorbed, while other solutes (such as hydrogen ions) are selectively secreted into the filtrate. In order to maintain these functions, the kidneys require a very high metabolic rate. They are known to utilize a fairly constant and relatively large amount of oxygen. Perhaps as a consequence of these factors, they are very sensitive to the effects of trauma and injury.

The sensitivity of the kidney is demonstrated during the course of many infections, diseases, and syndromes, that may not primarily involve the kidney. Any of these that change renal blood flow, can greatly affect kidney function. This influence is, again, due to the fact that perfusion and oxygen availability

are major variables of the state of the kidney. However, the exact pathogenesis of hypoperfusion and ischemic injury, is not yet known.

Some pathophysiology of the kidney is understood. Under conditions where the reabsorptive mechanisms fail, a polyuric condition can ensue and much or all of the filtered plasma will be excreted. In other cases, none of the plasma is filtered or all of the filtrate may be reabsorbed, resulting in anuria, during which no water, hydrogen ions, nor other solutes are excreted. Neither of these conditions is compatible with continued life of the individual, without supportive intervention.

The total mechanism of ischemic renal injury, as mentioned, is not understood. Moreover, this type of injury continues to be a major cause of frank kidney failure, especially among the young. When renal failure is permanent, there are only two treatments available. They are dialysis and transplantation. Dialysis does not resolve the problem, it only forestalls the inevitable. Although, ideally, transplantation provides a permanent solution to the problem of an otherwise fatal renal failure, it is fraught with complications.

Renal damage may be caused directly by a less-than-sufficient perfusion, as well as outright ischemia. The precise role of the two factors has not yet been well defined.

Perhaps the best documented periods of renal ischemia are seen in renal transplant work. Often, the re-implanted kidney does not function, presumably because the organ has, in some way,

lost its viability. Methods used to predict organ viability, have included measurements of: anoxia time and temperature (Angell et al, 1969); cell membrane potentials (Lambotte, 1970); surface pH (Dmochowski & Couch, 1966; Berman et al, 1970); PAH uptake and lysosomal enzyme release (Lotke & Schwartz, 1970); formazan production (Terasaki et al, 1967; Maginn, 1968; Ham et al, 1969); progression of lactate acidosis (Johnson, 1974); liberation of LDH (Liebau et al, 1971; Abouna, 1972; Jensen & Kemp, 1972; Kemp, 1972; Kohn & Ross, 1971); oxygen consumption (Bautista & Cohn, 1967); oxygen utilization (Lannon et al, 1967); renal blood flow (Ariyan et al, 1971); and loss of adenine nucleotides (Calman, 1974; Buhl, 1976a,b,c; Petterson, 1974; Bergstrom et al, 1971; Collstett, 1971; Keaveny, 1972).

According to Calman (1974) these methods of assessing viability are all based on the same presumed pathogenesis: organ failure when cell anoxia causes:

- a) inhibition of oxidative phosphorylation,
- b) a drop in adenine nucleotide content,
- c) an alteration in cell membrane potential,
- d) changes in surface and intracellular pH with a subsequent modification of the intracellular redox potential,
- e) consumption of any available oxygen, and
- f) eventual release of lysosomal enzymes.

Until recent work by Trump (1971, 1974, and 1976), Glaumann (1975a,b, and 1976), and their co-workers, a detailed analysis of structural changes as a function of the duration of ischemia, had

not been performed. Their studies suggest that energy coupling is, in fact, the crucial phenomenon and the one that fails irreversibly upon ischemic or anoxic injury.

Traditional models for the study of ischemia have involved opening the abdomen, isolating and clamping vessels, closing the abdomen for varying lengths of time, re-opening the abdomen, unclamping the vessels, and then assessing the damage 'due to ischemia'. It is our purpose to develop an acute surgical model in which we can directly control in vivo renal perfusion and assess parameters of renal function. Such a model would permit increases or decreases in renal arterial pressure, mimicking hypertension and hypotension, respectively. Total interruption of renal blood flow for varying lengths of time, would also be possible, without re-opening the abdomen.

The considerations implicit in developing such a model, include:

- a) choice of an animal species,
- b) choice of an anesthetic agent,
- c) how to minimize the effects of handling, and
- d) whether to hydrate and, if so, how much.

Although the ideal species for our purpose probably does not exist, we felt that the rabbit offered many advantages. These included: organ and vessel sizes permitting easy manipulation; no evidence of chronic renal disease in mature animals; availability of large numbers of genetically similar animals; relative consistency of internal anatomy; ease of handling; and modest cost of purchase and upkeep.

In the course of any general anesthesia, renal blood flow may be reduced as a result of hypotension and/or renal vasoconstriction. All anesthetic agents constitute myocardial depressants (Price, 1961). In sufficient quantities, they will produce hypotension, unless their effects are compensated by peripheral vasoconstriction (Mazze & Bunker, 1974). Some anesthetic agents (eg. cyclopropane or diethyl ether) seem to stimulate catecholamine release (Price et al, 1959). The resulting vasoconstriction will tend to support central blood pressure but will increase renal vascular resistance (Deutsch et al, 1966). Other anesthetic agents (eg. halothane and thiopental) do not appear to elicit the release of catecholamines (Price et al, 1959), but are associated with a moderate increase in renal vascular resistance (Deutsch et al, 1966). This increased resistance allows blood to be directed away from the kidneys to compensate for the anesthetic-induced hypotension. The result is some depression of renal function, but not as much as that which accompanies anesthesia with agents causing catecholamine release (Mazze & Bunker, 1974). Still other anesthetic agents (for instance, methoxyflurane) are considered to have indirect toxic effects upon the kidney (Crandell et al, 1966; Frascino et al, 1970; Mazze et al, 1971). The central nervous system depressants with alpha blocking capacity (for example, dehydrobenzperidol with fentanyl) fall into another group (Janssen et al, 1963). Gorman and Craythorne (1966) report no change in renal function and only slight myocardial depression with this so-called 'neuroleptanalgesia'. However, its superiority as a mode

of anesthesia is still contested (Doenicki & Kropp, 1976) and it is quite short-acting.

At present, barbiturates and halothane are two major anesthetic methods in widespread clinical use. Barbiturates are respiratory depressants, and respiratory arrest is commonplace where these are used without respiratory support (Lumb and Jones, 1973). Inhalation anesthesia is not often used with rabbits. The animals are very difficult to intubate (Murdock, 1969) and technical skill with expensive equipment is required to anesthetize them. Nevertheless, we chose to employ halothane as sole anesthetic.

There appear to be species differences in the response to halothane (Millar et al, 1969). In man, halothane anesthesia is associated with central sympathetic depression (Millar, 1971) and baroreflex depression (Duke et al, 1977). In the rabbit, while a partial central blockade of the barostatic reflexes by halothane has been demonstrated (Biscoe & Millar, 1966), halothane administration is associated with increased sympathetic activity (Millar, 1971). This increased sympathetic activity, however, seems to be ineffective in raising arterial pressure.

Induction of surgical anesthesia with halothane is rapid, usually being reached in humans, in 5-7 minutes with concentrations of 2.5% (Stephan & Little, 1961). Excited animals generally require more anesthetic (Lumb & Jones, 1973). Lindena et al (1978) demonstrated that excited animals also have increased levels of major metabolic enzymes in the circulation. Many experimenters have used premedication to counteract pre-operative excitement and

its consequent effects. We chose not to use these agents.

Halothane by itself, will slightly reduce blood pressure in the rabbit and cause a compensatory vasoconstriction, amplified by increased sympathetic activity. In the human, there is no sympathetic dilator nor parasympathetic innervation of the kidney (Mazze & Bunker, 1974). There are, however, abundant sympathetic constrictor fibers derived from the T₄ - L₁ segments of the spinal cord, via the celiac and renal plexuses (Mazze & Bunker, 1974). Assuming a similar pattern of innervation in the rabbit, we would expect its renal response to halothane to be similar, at least, to the human one.

Mazze and Bunker (1974) summarize the customary human renal response to anesthesia and surgery, as being characterized by depression of all measured function. This includes urine flow, glomerular filtration rate (hereafter referred to as GFR), renal blood flow (hereafter referred to as RBF), and electrolyte excretion. They suggest this generalized depression of renal function is influenced by four factors:

- a) the type and duration of the surgical procedure (Hayes & Goldenberg, 1963),
- b) the pre-operative physical status of the patient (Barry et al, 1964; Seitzman et al, 1963),
- c) blood volume, and fluid and electrolyte balance before and during surgery (Boba & Landmesser, 1961; Hutchin et al, 1961; Mazze & Barry, 1967), and
- d) choice of anesthetic agent (Gorman & Craythorne, 1966). The

approach in this study was to hold factors a, b, and d constant in an experimental system, permitting a study of the effects of factor c. Although unmentioned by Mazze and Bunker, a fifth factor which may influence renal function is the administration of premedications (de Boda & Sweet, 1944).

Reduced urine flow, as previously stated, has been almost universally accepted as an unavoidable companion to anesthesia and surgery. Barry et al (1964) demonstrated, for example, that anesthetic concentrations of from 0.5 to 3.0% halothane significantly depressed renal plasma flow, GFR, and urine flow, in fluid-restricted subjects. By contrast, they report that approximately normal levels of these parameters can be maintained, during light anesthesia, by sustained hydration. Cizek (1961), in a very comprehensive study in the rabbit, has established that food deprivation in this species consistently results in polydipsia and a high urine flow rate. Fasted rabbits should therefore, be well hydrated. But, how much fluid needs to be administered intra-operatively to rabbits in order to maintain hydration and, thusly, renal function? In this matter there appears to be great divergence of opinion.

Rabbits have a circulating blood volume of approximately 75 ml per kg. Beechwood et al (1964) in his renal studies in rabbits, administered from 1.5 to 4.0 ml fluid per minute per kg body weight, for more than 90 minutes (for the convenience of comparison, infusions are cited here in terms of ml/min/kg). This equals a volume of up to 360 ml per kg (or, 36% of total

body weight), or about five times the circulating blood volume. The intravenous fluid given, contained 20 mEq NaCl per liter and no serum electrolyte determinations were made. The animals were heparinized and of either sex. Our experience indicates that the female bleeds much more profusely than the male. Beechwood and his associates performed tracheostomies on their rabbits and exposed the left ureter through a flank incision. No estimate of blood loss was reported by these researchers, nor did they apparently determine either blood gases or hematocrits. Neither the infusion solution nor the animals were warmed. Urine from left kidneys reached flow rates of 2-3 ml per minute. This urine was collected and two samples were analyzed in most cases, but three samples were analyzed in some cases, without indicating what made the third collection occasionally possible. These animals might well have been hypervolemic, hyponatremic, hemodilute, hypothermic, polyuric, and dying of acidosis. The renal clearances from these animals, have been quoted (Biology Data Book, 1974) as normal renal clearances for rabbits.

Barraclough et al (1970), in their study of hypertonic saline and mannitol diuresis in the rabbit, administered 0.5 to 1.0 ml fluid per minute per kg body weight for up to 24 hours. Jorgensen et al (1972) in their study on molecular filterability in rabbit kidneys, infused from 0.5 to 1.0 ml fluid (physiological saline with additives of varying molecular weight) per minute per kg body weight, for up to 3 hours. The total infusion is about two and a half times the original circulating blood volume. Sudo et al

(1977) administered 1.2 ml per minute to rabbits weighing about 3 kg, during renal clearance studies. Meffan et al (1969) and Malinin and Hollerman (1972) do not mention any quantity of fluid administration to their rabbits during surgery. Nor do any of the above researchers make mention of any continuing assessment of the condition of their subjects by measuring arterial blood pressure, or pH. In fact, very few recent studies on rabbits during surgery demonstrate any concern for the potential effect of changes in these parameters. This is questionable in research involving a species so traditionally thought of as having a very sensitive renal system. Notable exceptions to this, are Lyrdal and Olin (1975) who administered a modest 0.06 ml electrolyte/infusion solution per minute per kg body weight to their rabbits during renal studies under anesthesia. They measured hematocrits, arterial blood pressure, blood gases and body temperature during their procedures examining the renal effects of surgical trauma.

Some investigators arbitrarily select an administration of fluid equal to some percentage of the body weight. Others replace urine volumes. A rationale for proposed fluid administration is almost never given. It was the purpose, therefore, of this study to ascertain whether there is an optimal intravenous administration of physiological saline, for acute renal studies in the halothane-anesthetized rabbit. The criterion employed to determine this was maintenance of the normal range of blood and urine parameters. This information was sought as a contribution to the creation of a stable rabbit model for renal studies during anesthesia.

CHAPTER II

MATERIALS AND METHODS

A. ANIMALS

Twenty-four male New Zealand White rabbits, weighing 2.7 ± 0.3 kg, were obtained from the Health Sciences Animal Center, of the University of Alberta. These had been purchased from a commercial breeder. They were kept in standard wire cages in a well ventilated room. Room temperature was maintained at about 22°C and the humidity was about 36%. The light cycle was from 7 am to 7 pm daily. Resting rabbits were fed a standard chow (Maple Leaf Mills, Master rabbit pellets) composed of 16% crude protein, 3% crude fat, 15% crude fibre, 0.65% salt, 1.2% calcium, 0.6% phosphate, and added vitamins A, D, and E. All rabbits were given tap water ad libitum.

The rabbits were randomly assigned to four surgical groups of six animals each. The only independent variable between the groups, was the amount of fluid administered intravenously during the surgical part of the experiment. Group 1 was the control group, and each animal received only enough normal saline to keep the venous cannula open (approximately 1.2 ml per hour). Group 2 animals received 0.5 ml saline per minute, or about 30 ml saline per hour. Group 3 animals received 1.0 ml saline per minute (60 ml per hour) and Group 4 animals received 2.0 ml saline per minute (120 ml per hour) throughout the procedure.

B. INSTRUMENTATION AND EQUIPMENT

For at least two days before surgery, urine was collected by means of a tilted tray slipped under the normal rabbit cage. Fecal material was retained by a screen, while urine drained into pre-weighed 1 liter glass collecting-bottles.

Just prior to surgery, each animal was weighed on a Fairbanks scale, model 45-1000KB.

Surgical anesthesia was induced and maintained with a Fluotec Mark 3 vaporizer used in a non-rebreathing mode. Halothane (2½%) was administered, through a close fitting facemask, in 0.6 liter per minute of a 1: 5 oxygen : compressed air mixture. Maintenance was similar except that the anesthetic concentration was reduced to 1%. Breathing was unassisted.

During surgery, the animal's temperature, ECG, and arterial blood pressure were recorded on a Beckman Type R Dynograph recorder. ECG is an abbreviation for electrocardiogram.

The animal's pre-operative temperature was maintained with a 100-watt lamp and a metal operating table warmed to 42° C by a circulating water bath (Heto type 623). The animal's temperature was monitored with a small animal rectal temperature probe (Yellow Springs Inst. Co., Yellow Springs, Ohio) inserted into the rectum. The probe was coupled to the recorder through a Beckman Thermistor Coupler type 9858.

The ECG was recorded from needle probes inserted under the sternal and left medial thigh skin with a third needle probe under the right medial thigh skin, acting as a ground. These probes were connected to a Beckman EKG Coupler type 9855 and thereby to the

recorder. The recorder was coupled to a Tektronic Type 561A oscilloscope to permit a visual display of the ECG.

Systemic blood pressure was monitored by placing an Argyle 3 $\frac{1}{2}$ Fr Umbilical Artery Catheter in the left femoral artery. This catheter was connected by non-elastic polyethylene tubing to a Statham pressure gauge, type PR 23 5D 300. This latter was coupled to the recorder with a Beckman Strain Gage Coupler type 9803.

Urine was collected during surgery via a Bard 3 Fr whistle-tip ureteral catheter. The catheter was cut off at about 15 cm and fitted with a 27 gauge needle connected to an air-powered sump drain. The air and any urine passed through a short piece of polyethylene tubing into small pre-weighed collection vials.

C. PROTOCOL

Each rabbit was familiarized with the experimenter through direct contact over a period of at least 4 days. At least two 24 hour urine volumes were collected from each subject. This urine was weighed and analyzed for electrolytes and osmolarity. At the end of each 24 hour collection period, a venous blood sample, for hematocrit determination, was taken from the ear. During the 24 hours before surgery, each animal was fasted, but allowed water ad libitum. Urine collection periods were begun each day at 10:00 am, because of the convenience of initiating surgical procedures in the late morning and because experience had shown that little or no urine was voided during this time. This permitted the cleaning of the collection trays, the taking of hematocrit

blood samples, and the transferring of animals, without adjusting the starting time of the collection periods.

After the 24 hour fast, the rabbits were brought to the laboratory in a closed cardboard box. They were taken out of the box and placed prone on the pre-warmed operating table. Then, cradled in the left arm of the experimenter between chest and table, the animals' faces (including the eyes) were covered in the anesthetic mask. Each was held firmly until anesthetized. After about five minutes, the face mask was taped securely to the unconscious animal.

A 23 guage short bevel needle, on a heparinized syringe, was inserted into the central artery of the left ear and about 0.75 ml of arterial blood was drawn for blood gas measurements. A further 1.5 ml sample of unheparinized venous blood was taken for electrolyte and osmolality analysis, transferred to a 7 ml test tube, and allowed to clot.

The animals were then placed in a supine position, the limbs were secured, and the lower half of the abdomen and medial aspect of each hindlimb was shaved closely. The left medial upper hind leg was palpated for a pulse and then a three centimeter incision, starting at the abdominal junction, was made over the left femoral artery. With blunt dissection, the incision was carried through the underlying layers of fascia. The sartorius muscle was retracted cranially and the gracilis muscle caudally, to expose the femoral vein, nerve, and artery. These were carefully dissected apart and a 1 cm length of the artery was looped cranially and caudally

with number 00 cotton. The caudal loop was tied and a serrifine forceps was applied just caudal to the cranial loop. The vessel was nicked with iris scissors between loops and, using a stay stitch of six-0 silk on either side of the nick, a heparinized-saline filled catheter was inserted cranially into the femoral artery. The vascular clamp was removed and about 12 cm of the catheter were inserted into the artery. This brought the tip of the catheter up the descending aorta to about the level of the left kidney. The catheter was secured in place with two ties of number 00 cotton. The systemic blood pressure was monitored continuously from this cannula, and recorded.

A 1 cm length of the femoral vein was then looped twice, in continuity, with number 00 cotton. Again, the caudal loop was tied and a 20 gauge Argyle Medicut cannula was placed in the femoral vein, secured with cotton ties, and fitted to the intravenous line of a Buretrol 100 ml Burette solution administration set. After intravenous fluid flow was established, the femoral cut-down site was packed with saline-soaked sponges.

A six to seven centimeter midline incision was made caudally from the umbilicus through the skin, fascia and linea alba, into the abdomen. The cranial tip of the urinary bladder was grasped and the bladder was pulled from the abdomen. The abdominal incision was packed off with saline soaked sponges. The bladder was emptied of urine (if any) with a syringe, and was incised longitudinally on the ventral surface through a relatively avascular plane. The ureteral catheter was passed into the left ureter

through the left ureteral papilla to a level of about 10 cm. The catheter was secured inside the ureter by a peri-ureteral tie of number 00 cotton just cranial to the junction of the ureter and the bladder.

The abdomen was closed, skin edges being held together with Allis forceps, and covered with saline-soaked sponges. The halothane concentration was reduced to the maintenance level. Urine was collected continuously from the ureteral catheter.

Three hours from the time of induction, appropriate venous and arterial blood samples were again taken for determination of blood gases, osmolarity, packed cell volume, and electrolytes.

In cases where a steady urine flow occurred for forty minutes, renal function studies were performed. Using an LKB Perpex peristaltic pump (model 10202) an infusion was made at a rate of 0.55 ml per minute, into a marginal vein of the left ear. The infusion solution contained 6 μCi ^{14}C -PAH and 150 μCi ^3H -inulin in 25 ml of a solution containing 0.1% of both PAH and inulin in normal saline. Radioactive chemicals were purchased from New England Nuclear, of Boston, Mass. The inulin was ^3H generally labelled, catalogue number NET-314 L, with a specific activity of 1.0 mCi per 2.6 mg. The PAH was p-(glycyl-1- ^{14}C)-aminohippurate, catalogue number NEC-563, in a 0.01 N HCl solution, with a specific activity of 0.05 mCi per 0.22 mg.

Two twenty minute urine samples were collected beginning 2 minutes from the start of the infusion. A 1 ml blood sample was drawn from the right ear at the beginning of each collection, and

at the end of the second collection. The results of isotope analysis of these samples were used to calculate renal clearances according to the following formulae:

Effective Renal Plasma Flow (ERPF)

= Clearance_{PAH} at low plasma concentrations of PAH

$$= U_{PAH} \cdot V_U / P_{PAH}$$

where U_{PAH} is the concentration of radioactive PAH in the urine,

P_{PAH} is the concentration of radioactive PAH in the plasma, and

V_U is the rate of urine production.

Glomerular Filtration Rate (GFR)

= Clearance_{In}

$$= U_{In} \cdot V_U / P_{In}$$

where U_{In} is the concentration of radioactive inulin in the urine,

P_{In} is the concentration of radioactive inulin in the plasma, and

V_U is the rate of urine production.

D. METHODS

Serum and plasma for serum electrolytes, isotope counting, and osmolarity measurements were prepared by centrifuging venous blood in a test tube for 5 minutes at 1000 rpm in an IEC Model CL Clinical Centrifuge (rotor type 213).

Electrolyte concentrations were determined in both serum and

urine using an Instrumentation Laboratories Flame Photometer Model 143 for the sodium and potassium, and a Buchler-Cotlove Direct Reading Chloridometer Model 4-2008 for the chloride.

Hematocrits were determined by taking venous blood in Dade heparinized hematocrit tubes. The tubes were centrifuged in an International Equipment Micro-capillary centrifuge (model MB) for 4 minutes. The length of the column of packed cells was divided by the length of the entire sample to give per centage packed cell volumes.

Osmolarities of serum and urine were determined using a Precision Systems Osmette S Model 4002 Automatic Osmometer.

Blood gases were determined with a Radiometer Blood Micro System BMS 3 and Radiometer Acid-Base Analyzer PHM 71.

Isotope content of plasma and urine was determined by oxidizing a 200 μ l sample of either in a Packard Model 306 Sample Oxidizer followed by counting in a Searle Mark 3 Liquid Scintillation Counter, for ten minutes.

Statistical analyses were performed according to Sokal and Rohlf (1969) using tables from the Handbook of tables for Probability and Statistics (1968).

CHAPTER III

RESULTS

FASTING

During fasting, there was an increase in the coprophagic activity of all rabbits. This produced a noted reduction in hard fecal waste under the cages. The rabbits also seemed to drink more, but this was difficult to document because the rabbits allowed water to dribble while they drank from the graduated bottles.

Fasting for 24 hours caused an increase in urine production from 4.9 ± 2.5 ml/hr in the resting rabbit to 7.1 ± 4.7 ml/hr in the fasting animal (results will all be given as the mean value plus or minus the standard deviation). This increase is significant ($p < 0.05$). The 24 hour fast caused a slight increase in the venous hematocrit from $43.2 \pm 2.7\%$ in the resting to $44.3 \pm 2.7\%$ in the fasting animal, an insignificant increase ($p > 0.05$).

Urinary concentrations of sodium, chloride, and potassium dropped during the 24 hour fast. The urinary sodium concentration decreased significantly ($p < 0.001$) from 63.3 ± 31.2 mEq/l in the resting rabbit to 25.3 ± 18.7 mEq/l in the fasting animal. Urinary chloride concentration decreased significantly ($p < 0.01$) from 70.6 ± 43.4 mEq/l in the resting to 33.7 ± 33.4 mEq/l in the fasting state. Urinary potassium concentration dropped significantly ($p < 0.001$) from 168 ± 70 mEq/l in the resting to 68 ± 40 mEq/l in the fasting state. The rates of sodium, chloride, and

potassium excretion, were also reduced by fasting. Sodium excretion dropped significantly ($p < 0.01$) from 4.4 ± 2.3 $\mu\text{Eq}/\text{min}$ in the resting to 2.5 ± 1.8 $\mu\text{Eq}/\text{min}$ in the fasting state. Chloride excretion dropped significantly ($p < 0.05$) from 5.2 ± 2.9 $\mu\text{Eq}/\text{min}$ in the resting to 3.0 ± 3.5 $\mu\text{Eq}/\text{min}$ in the fasting state. The slightly greater excretion of chloride over sodium in the resting state or the fasting state, is not significant. Potassium excretion dropped significantly ($p < 0.001$) from 12.0 ± 4.8 $\mu\text{Eq}/\text{min}$ in the resting to 6.0 ± 2.3 $\mu\text{Eq}/\text{min}$ in the fasting state.

Fasting also reduced urine osmolarity significantly ($p < 0.001$) from 1204 ± 552 osmol/l in the resting, to 542 ± 300 osmol/l in the fasting state.

ANESTHESIA

In an earlier series of experiments, an attempt was made to determine an effective dose of atropine in rabbits. The effects of large intravenous dosages (0.1 mg of atropine sulphate) were difficult to distinguish from the effects of smaller subcutaneous injections (0.05 mg), or no atropine at all. In this series of experiments, no premedications of any kind (including atropine to avert potential bradycardia) were used. During the induction of anesthesia, animals properly conditioned through familiarization, did not hold their breath nor struggle appreciably. Anesthetized animals breathed deeply and regularly at a minute respiration rate of 62 ± 21 . Over a three hour anesthetic period, breathing became more shallow and rapid, although it remained quite regular.

After induction of anesthesia, the heart rate was regular (311 ± 27 beats per min) and the ECG was normal in all cases where the ECG leads were functioning correctly. There was a slight reduction in heart rate among control rabbits and those receiving 0.5 or 1.0 ml saline per minute (293 ± 21 , 302 ± 25 , and 289 ± 20 beats/min, respectively), but this was not significant. There was a highly significant ($p < 0.01$) reduction in the heart rate after three hours, among rabbits in the group receiving 2.0 ml saline per minute (253 ± 50 beats/min). Changes in heart rate are demonstrated in Figure 1.

Systolic blood pressure (Fig. 2) for all rabbits, as a group, was 72 ± 9 mm Hg after anesthetic induction. During the three hours after anesthetic induction there was a significant systolic pressure drop (to 61 ± 10 mm Hg) in the control group ($p < 0.05$). Systolic blood pressure in the groups receiving 0.5 or 1.0 ml saline per minute, did not change significantly (71 ± 14 and 74 ± 10 mm Hg, respectively). In the group receiving 2.0 ml saline per minute there was a systolic pressure drop (to 60 ± 25 mm Hg), but it was not significant. Diastolic blood pressure (Fig. 3) after induction of anesthesia was 43 ± 12 mm Hg. Only the group receiving 2.0 ml saline per minute showed a drop (to 32 ± 14 mm Hg) in diastolic blood pressure, but this drop did not prove to be significant.

SURGERY AND FLUID ADMINISTRATION

Only eight rabbits (of the twenty-four) produced any urine

Figure 1

Heart rate 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial heart rate. Initial rate is shown as the mean plus or minus the standard deviation ($n = 24$) and rates after 3 hours are shown as individual values.

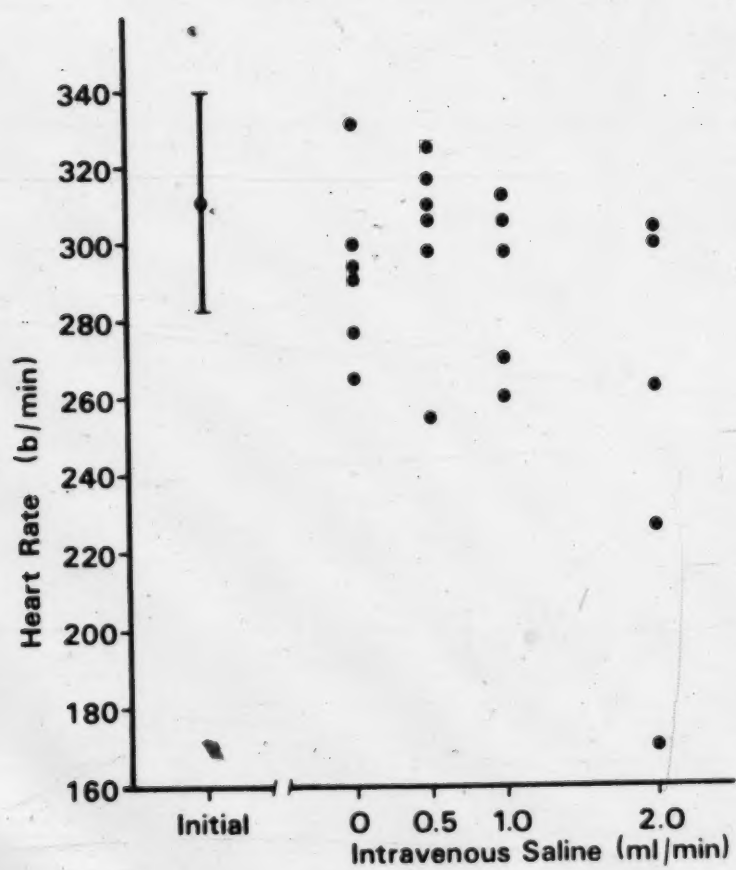


Figure 2

Systolic blood pressure 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial systolic blood pressure. Initial pressure is shown as the mean plus or minus the standard deviation ($n = 23$). Pressures after 3 hours are shown as individual values, for a total of 21 observations.

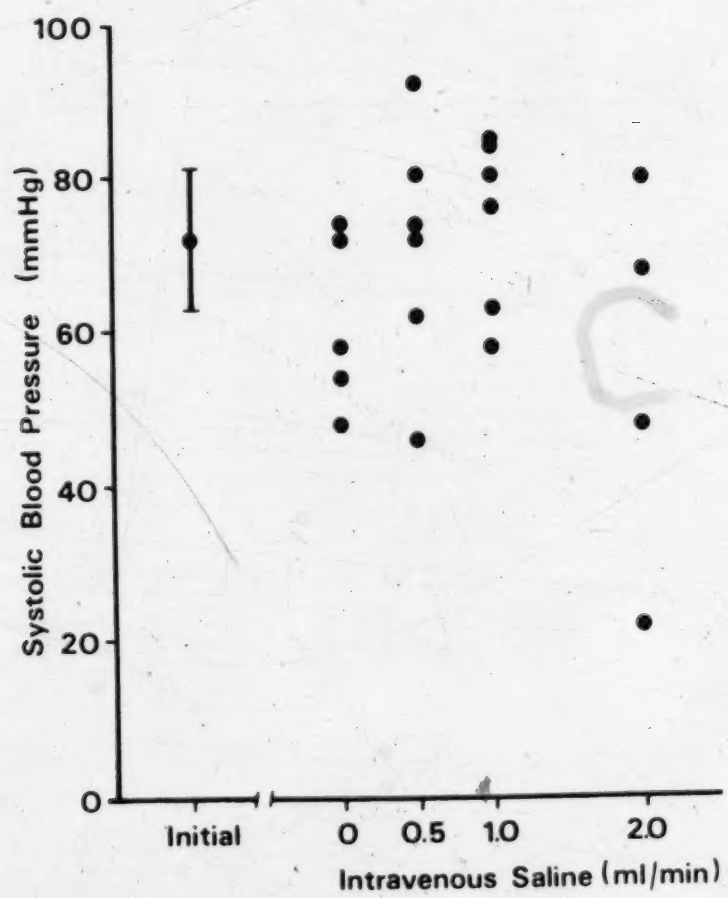
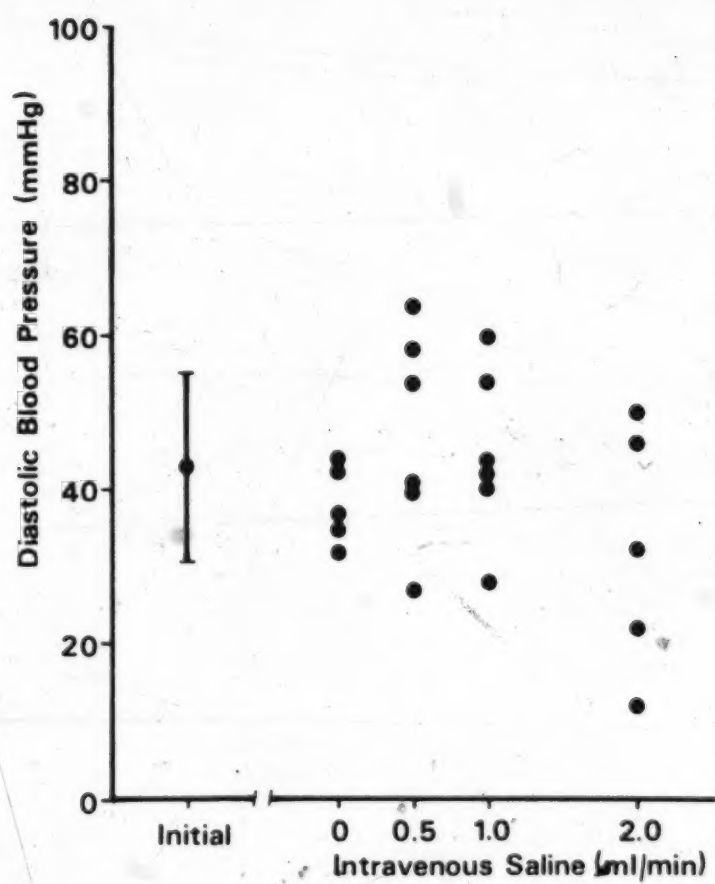


Figure 3

Diastolic blood pressure 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial diastolic blood pressure. Initial pressure is shown as the mean plus or minus the standard deviation ($n = 23$). Pressures after 3 hours are shown as individual values.

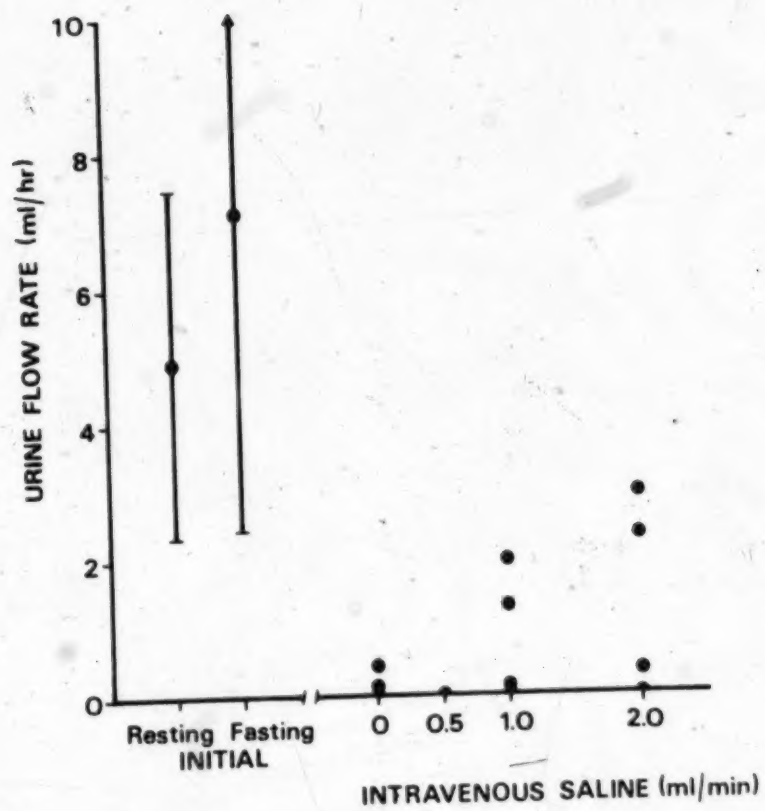


during the course of the experiment. Of these, only one (a member of the 2.0 ml group) produced urine throughout the entire procedure. The other seven stopped producing urine after a period ranging from 5 to 85 minutes. Rabbits in the control group produced urine for an average of 5.8 minutes, while no rabbit in the group receiving 0.5 ml saline per minute produced any urine. Rabbits in the groups receiving 1.0 and 2.0 ml saline per minute produced urine for an average of 21.2 and 40.8 minutes, respectively. Because of the lack of sustained urine flow, only one clearance study was completed, though several were started. Figure 4 demonstrates that urine production was severely reduced during anesthesia and surgery in the rabbit. The average urine production during surgery for all animals including those that did not produce urine, was 0.40 ± 0.85 ml/hr. The number of animals that produced no urine at all, is indicated by the standard deviation being greater than the mean value. Doubling unilateral flows would bring the urine production rate into the low pre-operative range, only in the cases of some of the rabbits receiving 2.0 ml saline per minute.

Among those rabbits that did produce urine, sodium and chloride excretion tended to be higher while urine was being produced, than either the resting or the fasting state, in animals receiving either of the two higher infusion rates. Unilateral sodium excretion from animals producing any urine during surgery, was 3.1 ± 2.8 μ Eq/min in animals receiving 1.0 ml and 5.2 ± 3.7 μ Eq/min in animals receiving 2.0 ml saline per minute. Unilateral chloride excretion from animals producing urine during surgery, was $3.0 \pm$

Figure 4

Total unilateral flow vs. intravenous saline infusion rate and initial bilateral urine flow in the resting and fasting rabbit. Initial urine flows in the resting and fasting rabbits are shown as the mean plus or minus the standard deviation ($n = 24$). Total urine flows are shown as individual values based upon total unilateral urine volume produced within the two hours after ureteral cannulation. Each of the four rates of saline infusion was administered to 6 animals; where fewer than 6 results are displayed, animals unaccounted for, also, produced no urine. Accordingly, in the control, 0.5 ml, 1.0 ml and 2.0 ml groups, 4 animals, 6 animals, 3 animals, and 3 animals, respectively, produced no urine.



2.7 $\mu\text{Eq}/\text{min}$ from animals receiving 1.0 ml and $4.5 \pm 3.7 \mu\text{Eq}/\text{min}$ from animals receiving 2.0 ml saline per minute. A slightly greater excretion of sodium than chloride seems apparent in the anesthetized state, but it is not significant. Unilateral potassium excretion tended to be lower ($1.2 \pm 1.0 \mu\text{Eq}/\text{min}$) in those animals that produced urine during anesthesia, than comparable values in resting or fasting rabbits (bilateral excretions of 12.0 ± 4.8 and $6.0 \pm 2.3 \mu\text{Eq}/\text{min}$, respectively). Serum potassium levels, however, seemed to increase (from an initial value of $3.9 \pm 1.0 \text{ mEq}/\text{l}$ to $5.5 \pm 1.7 \text{ mEq}/\text{l}$ after 3 hours of anesthesia and surgery).

Sodium concentration in the urine that was produced during surgery, averaged $147 \pm 32 \text{ mEq}/\text{l}$. The concentration of this ion in urine from resting and fasting animals was 63 ± 31 and $25 \pm 19 \text{ mEq}/\text{l}$, respectively. However, the concentration of sodium ion in the serum just after anesthetic induction was $164 \pm 15 \text{ mEq}/\text{l}$ and this concentration had not changed appreciably ($161 \pm 15 \text{ mEq}/\text{l}$) after three hours of anesthesia and surgery, despite fluid administration. Chloride concentration in urine produced during surgery and anesthesia averaged $132 \pm 37 \text{ mEq}/\text{l}$. The concentration of this ion in serum was initially $123 \pm 11 \text{ mEq}/\text{l}$ and was not appreciably different ($128 \pm 9 \text{ mEq}/\text{l}$) after 3 hours of anesthesia and surgery. Pre-operative concentrations of chloride ion in urine were $71 \pm 43 \text{ mEq}/\text{l}$ and $34 \pm 33 \text{ mEq}/\text{l}$ from resting and fasting animals, respectively.

Serum osmolarity was initially $343 \pm 25 \text{ osmol}/\text{l}$ and had not significantly changed after 3 hours of anesthesia and surgery

(349 ± 26 osmol/l) despite fluid administration. Urine osmolarity during anesthesia and operation (522 ± 51 osmol/l) was lower than that of the urine from resting rabbits (1204 ± 552 osmol/l), but within the range of osmolarities of urine from fasting rabbits (542 ± 300 osmol/l), and the rabbits had, of course, been fasted.

Figure 5 shows that the pH of arterial blood (initially, 7.354 ± 0.072) was severely reduced ($p < 0.01$), during surgery, only by a saline infusion of 2.0 ml per min (pH of 7.030 ± 0.202). The pH of arterial blood was not significantly reduced in control animals nor in those receiving an infusion of 0.5 or 1.0 ml per minute (pH's of 7.330 ± 0.050 , 7.318 ± 0.064 , and 7.058 ± 0.328 , respectively). More observations would be required in order to determine whether an infusion of 1.0 ml/min actually does reduce arterial blood pH. The pCO_2 of arterial blood (Fig. 6) did not significantly change (from 41.7 ± 7.0 mm Hg, initially) in rabbits receiving 0.5 or 1.0 ml saline per minute (38.7 ± 10.6 mm Hg and 95 ± 75 mm Hg, respectively). However, this parameter was significantly reduced ($p < 0.01$) among rabbits receiving no appreciable intravenous fluid (25 ± 2.5 mm Hg), and significantly elevated ($p < 0.01$) in those receiving 2.0 ml saline per minute. Arterial blood pCO_2 in this latter group was 90.5 ± 23.6 mm Hg. Figure 7 demonstrates that the pO_2 of arterial blood during surgery (initially, 125 ± 22 mm Hg) was severely reduced ($p < 0.01$) only among rabbits receiving 2.0 ml intravenous saline per minute (71 ± 24 mm Hg).

The intraoperative venous hematocrit was, also, influenced

Figure 5

Arterial blood pH 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial arterial blood pH. Initial pH is shown as the mean plus or minus the standard deviation ($n = 9$). Blood pH values after 3 hours are shown as individual values.

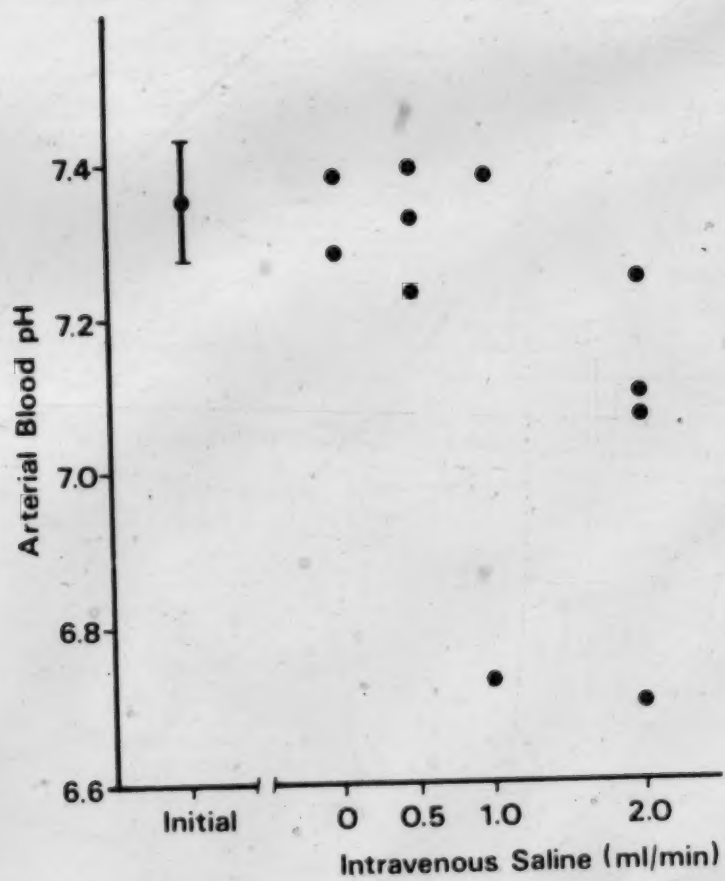


Figure 6

Arterial blood pCO_2 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial arterial blood pCO_2 . Initial pCO_2 is shown as the mean plus or minus the standard deviation ($n = 9$). Blood pCO_2 values after 3 hours are shown individually.

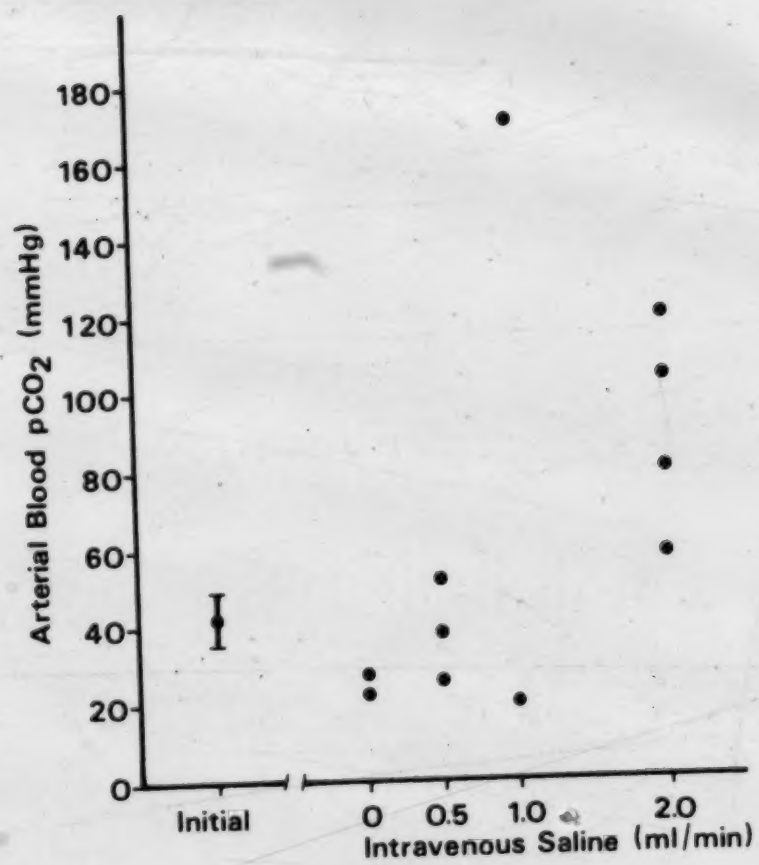


Figure 7

Arterial blood pO_2 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial arterial blood pO_2 . Initial pO_2 is shown as the mean plus or minus the standard deviation ($n = 9$). Blood pO_2 values after 3 hours are shown individually.

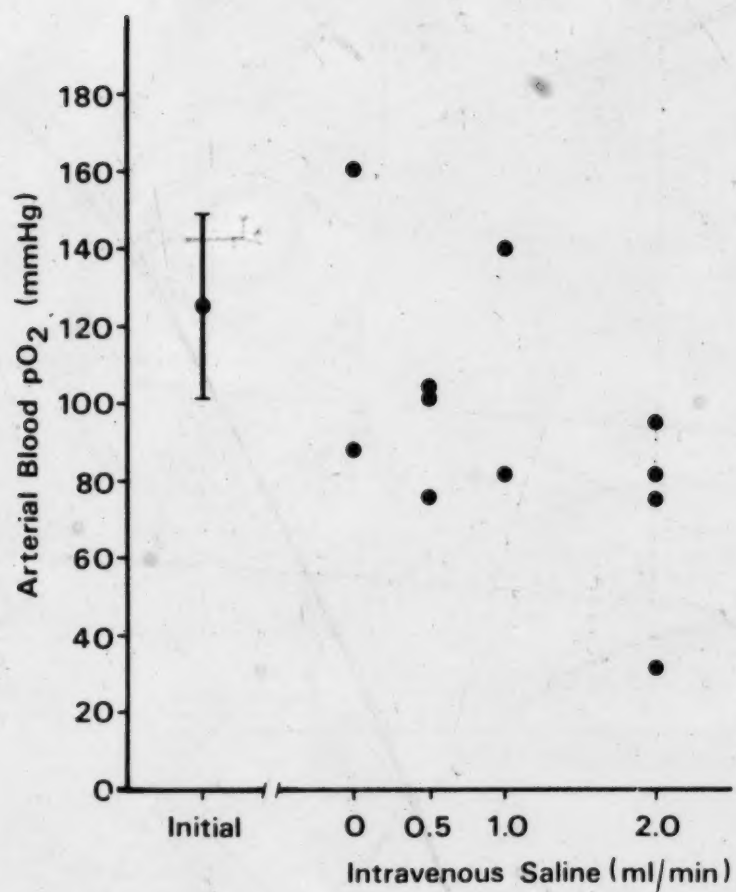
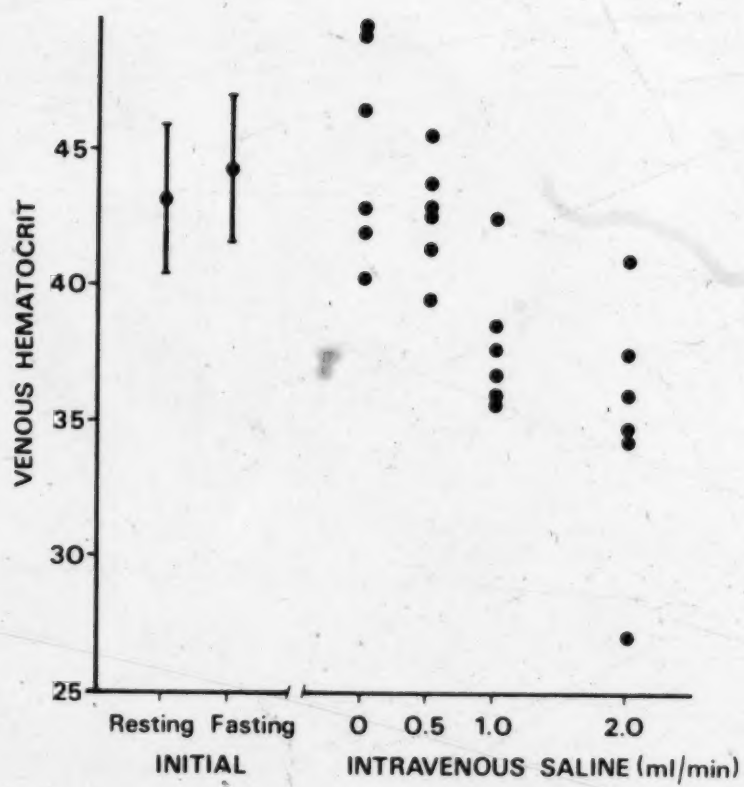


Figure 8

Venous hematocrit 3 hours after anesthetic induction vs. intravenous saline infusion rate and initial venous hematocrit in the resting and the fasting state. Initial hematocrits in the resting and fasting states are shown as the mean plus or minus the standard deviation ($n = 24$). Hematocrits after 3 hours are shown as individual values.



by saline administration. Figure 8 indicates that only in rabbits receiving 1.0 ml or 2.0 ml saline per minute intravenously, was there a noticable drop in the hematocrit (to $37.9 \pm 2.3\%$ and $35.2 \pm 4.2\%$, respectively, from $44.3 \pm 2.8\%$ in the fasted animal). This drop was highly significant ($p < 0.001$) in both cases. There was no correlation, whatever, between the fasting rabbits' hematocrit and urine production during anesthesia and surgery.

From the single successful attempt to perform a clearance study, there are interesting results. The urine production was, in this case, 0.045 ml/min. The hematocrit was 34.8%. Inulin clearance was 1.80 ml/min, and PAH clearance was 8.47 ml/min. Using the hematocrit and the PAH clearance, an effective renal blood flow of 13.0 ml/min could be calculated.

CHAPTER IV

DISCUSSION

Before discussing the results of this study, one point should be clarified. Saline with a sodium chloride content of 0.9% contains approximately 154 mEq NaCl per liter. Human serum contains from 135 - 145 mEq sodium and 95 - 105 mEq chloride per liter. This means that 'physiological' saline is not physiological. Neither is it chemically a 1 N solution, though it is referred to as 'normal' saline by many investigators oriented toward fields other than chemistry. In infusing this solution, one should be particularly aware that there is a much higher chloride concentration in this solution than in normal human serum.

FASTING

Fasting was necessary to overcome the difficulties encountered in earlier experiments while performing abdominal surgery on animals with a full digestive tract. Such rabbits showed a strong pressor response to manipulation of the viscera, with an often-fatal drop in blood pressure. Some animals (for example, the dog) tend to become oligodipsic and dehydrated upon fasting. Rabbits apparently become polydipsic during a fast (Cizek, 1961).

From the observed increase in rabbit coprophagy during fasting, it seems likely that Murdock's observation (1969) of full

stomachs in rabbits even after five days of fasting, is due to reconsumed fecal material, rather than slow digestion of food. Food deprivation for 24 hours did, indeed, cause rabbits to become polydipsic and diuretic, as Cizek (1961) had demonstrated, but produced no change or a slight increase in the venous hematocrit. This suggests the possibility that food deprivation for 24 hours may slightly dehydrate the rabbit. The concomitant drop in urinary electrolyte concentration, is not simply a dilutional effect due to the increased urine volume, since the rates of electrolyte excretion were also reduced by fasting. The reduction in urinary electrolyte concentration is also reflected in a drop in urine osmolarity. This means, in summary, that the fasted rabbit conserves electrolytes, probably in response to the severe reduction in electrolyte intake from the diet.

ANESTHESIA

Rabbits seem resistant to the effects of atropine. Godeaux and Tønnesen (1949) reported that rabbits tolerate very large doses of atropine, because many rabbit livers contain high levels of an enzyme which later became known as atropine esterase, which rapidly destroys the drug. Our results are consistent with such an explanation. The use of such pre-medications would only have complicated our research.

Without any pre-medications, rabbits can be successfully anesthetized without visible stress by inhaled halothane concentrations of 2½%. Our value (62 ± 21) for the rate of respiration

in anesthetized animals does not differ greatly from that of 51 breaths per minute, reported by Weisbroth et al (1974) in the resting rabbit. Weisbroth, also, reports that the resting heart rate in the rabbit is 306 - 333 beats per minute. Arrington and Kelley (1976) report a range of 123 - 304 beats per minute. Our range, in the just-anesthetized animals, is from 283 - 339 beats per minute, which does not differ greatly from the reported resting measurements. This range of heart rates was not significantly changed, after 3 hours anesthesia with surgery, among animals receiving 0.5 ml saline per minute. Heart rates were significantly reduced, however, among animals receiving 2.0 ml saline per minute, and animals in this group show greatly increased statistical variance of heart rate after 3 hours. The mechanism by which large saline loads reduced the heart rate during anesthesia and surgery, is not entirely clear. Ledingham (Morson, 1977) has suggested a mechanism that may be responsible. He states that acidosis causes a reduction in the formation of 2:3 diphosphoglycerate. When the concentration of 2:3 DPG, a hemoglobin ligand, in the red blood cell drops, oxygen binding increases and less oxygen is released to the tissues. The acute response is a small reduction in mixed venous oxygen tension. This is reversed gradually by an increase in cardiac output; a fall of 4 mm Hg in the mixed venous oxygen tension would require a doubling of cardiac output to maintain the same oxygen supply. This imposes a considerable load on a myocardium that is already stressed by anesthesia and surgery. Myocardial performance in the face

of hypervolemia might well be reduced accordingly.

Cardiac output is calculated by multiplying the heart rate by the cardiac stroke volume. Westermarck and Wahlin (1969) consider lowered cardiac output a more important cause of halothane hypotension, than reduction of peripheral vascular resistance. If this is correct, then halothane hypotension is primarily due to a reduction in stroke volume, since we found no significant reduction in heart rate just after induction, but there was a significant reduction in arterial blood pressure (normally, 110/80 according to Weisbroth et al; our just-anesthetized rabbits' pressures were 72 ± 9 / 43 ± 12 mm Hg).

SURGERY AND FLUID ADMINISTRATION

Two thirds of all the rabbits in the experiment, displayed complete anuria during surgery. Increased ureteral pressure of any significance would have been accompanied by high sodium re-absorption (Kiil & Aukland, 1961; Suki et al, 1971) which was not observed in our anesthetized rabbits. The ureteral catheter, therefore, cannot be blamed for the anuria, especially in view of the eight cases where urine was produced. The anuria might have been influenced by the femoral cut-down and stimulation of the femoral nerve. Cort and Barron (1948) found that stimulating the central end of a cut sciatic nerve, resulted in impulses of the same frequency in the splanchnic nerves. Goodwin et al (1949) produced several cases of bilateral renal ischemia and anuria, by stimulating the sciatic nerve, in both dogs and rabbits.

Goodwin also reports that splanchnic stimulation produces an outpouring of catecholamines (with mainly an adrenaline/nor-adrenaline effect) into the circulation (see also Elliot, 1912), with a subsequent renal vasoconstriction. Vasoconstriction due to nerve involvement has been considered unlikely during deep surgical anesthesia, since there was thought to be reduced sympathetic tone. However, in view of Millar's observation (1971) that halothane in the rabbit actually increases sympathetic activity, it is possible that the nerves may be involved in catecholamine release. In any case, opening the abdomen, handling the viscera, and operating upon the lower urinary tract (in spite of great care) are probably far more important causes of splanchnic stimulation and catecholamine release, than femoral nerve stimulation.

The anuria mechanism is also, undoubtedly, related to the low arterial blood pressures caused by halothane anesthesia. Renal autoregulation can be abolished by mean arterial blood pressure lower than 80 mm Hg (Leighton et al, 1977). Below this pressure, GFR, RBF, and urine flow, are directly related to the blood pressure, but according to research in the dog (Shipley & Study, 1951), mean arterial pressures of greater than 60 mm Hg should permit urine production. Our experiment did not demonstrate this: animals with mean arterial blood pressures of more than 60 mm Hg did not necessarily produce urine, nor did animals that produced urine necessarily have arterial blood pressures greater than 60 mm Hg. If the renal arteriolar blood pressure

is reduced lower than the systemic arterial blood pressure (of say, 82/52), by adrenaline/noradrenaline-mediated vasoconstriction, there may be very little production of glomerular filtrate. Furthermore, this extremely low filtrate volume may be almost entirely reabsorbed in the distal tubules and collecting ducts, due to increased ADH secretion. Adrenaline may stimulate increased ADH secretion (Papper & Ngai, 1956), and the result of all of these factors would be a negligible production of urine.

In cases where urine was produced, splanchnic stimulation and other causes of catecholamine release may not have been severe enough to cause adrenaline-mediated vasoconstriction to the point of terminating urine flow. In such cases, the urine production was still reduced, probably due to the abolition of autoregulation by hypotension, with a subsequent urine production that was directly related to the arterial blood pressure.

Part of the hypotension in our experiment may be attributed to the sequestering of fluid to the 'third space' due to the trauma to tissues, during surgery. This was not a major cause of the hypotension, however, since the venous hematocrit in animals receiving no appreciable intravenous fluid, was not significantly increased. We assume that there was some surgical trauma to tissue and, in fact, all animals tested demonstrated the expected slight increase in serum potassium levels.

Adequate urine output has been referred to as the 'poor man's cardiac output computer' (Howells, 1977). The concept, that specific urinary volumes reflect adequate hydration (Voss, 1976), is widespread among clinicians. There is, therefore, the

tendency to overhydrate in an effort to achieve arbitrarily established rates of urine production. Beechwood et al (1964) and others seem to have done this. In our study, fasting tended to increase urine production, but may also have dehydrated the animals a little (the hematocrit rose slightly -- a larger number of observations would be required to establish whether this is significant). Large intraoperative saline administrations also tended to increase urine production, but were accompanied by complications. We observed little difference between urine and serum concentrations of sodium or chloride, suggesting little or no selective reabsorption of these ions. This, together with the observed low urine osmolarity, is typical of vasomotor nephropathy. This does not mean that none of the filtrate was reabsorbed, however, but certainly indicates that blood was probably not shunted towards the juxtamedullary nephrons with their greater sodium reabsorptive capacity, at least in the cases where urine was produced. Saline infusions are generally said to increase sodium excretion independent of the filtered load, mineralo-corticoids, ADH, dilution of plasma proteins, or angiotensin (Blake & Jurf, 1968). As sodium intake is increased, nevertheless, the production of aldosterone (a mineralo-corticoid) is decreased (Valtin, 1973). This leads to decreased tubular reabsorption of sodium, but whether this mechanism is uniquely responsible for the electrolyte concentrations we observed, is not yet established.

Crepeau et al (1977) showed that urinary excretion of

hydrogen ion increases during metabolic acidosis, and suggest that this may be due to increased chloride availability at renal sites of hydrogen secretion. They report a greater loss of chloride than sodium in the urine during control, metabolic acidosis, or conditions of extracellular volume expansion, in the unanesthetized human. The only major pH regulatory action of the kidney that is depressed during or after a major operative procedure, is the differential excretion of chloride during intravenous saline infusion (Moyer, 1950). Our results do not contradict this. Rather, they suggest an insignificantly higher secretion of sodium. A larger number of observations would be required to establish whether this difference is real. Moyer claims that if chloride is not excreted significantly faster than sodium, a dilutional acidosis (Shires & Holman, 1948) may be induced. Animals in our group infused with 2.0 ml saline per minute, seem to have developed such an acidosis, reflected in their decreased arterial blood pH and increased pCO_2 values. From animals receiving an infusion of 1.0 ml/min, the blood gas observations are not numerous enough to allow conclusions. Blood gas observations were, in fact, made on only the last eleven animals used in the study. Hence, only limited conclusions can be drawn. Animals receiving no intravenous fluid seemed to become slightly alkalotic after 3 hours (they showed significant reductions in arterial blood pCO_2). This may be due to a decreased perfusion of the peripheral tissue with accumulation of metabolic by-products there, rather than in the central system. In addition to

contributing to dilutional acidosis, infusion of 2.0 ml saline per minute also caused a significant reduction in the pO_2 of arterial blood. Earlier experience had indicated that the use of 1:5 oxygen:air during anesthesia, produced arterial blood pO_2 values in the upper normal range for rabbits. Yet rabbits in the 2.0 ml group developed some very low pO_2 values. This may be a result of diluting the red cell (primary carriers of oxygen) concentration in the blood, since both 1.0 and 2.0 ml saline infusions significantly reduced the hematocrit. Another explanation is, that large fluid loads may permit pulmonary edema and thereby compromise respiration and oxygen availability.

Moyer (1950) suggests that Hartman's solution will not cause the dilutional acidosis commonly associated with sodium chloride solutions. Ringer's lactate solution has also been suggested, but it has been concluded that since some patients might not be able to metabolize the lactate, a further acidotic effect might be contributed. Lindeman and Papper (1975) state that there is no evidence favoring Ringer's lactate over any other balanced salt solution or sequential use of non-combination solutions.

Beechwood et al (1964) achieved urine productions in anesthetized rabbits, of 2-3 ml/min per kidney. Barraclough et al (1970), Jorgensen et al (1972), and Sudo et al (1977) apparently obtained urine production in their surgical rabbit-preparations, but none of the three mentioned a specific rate of flow. Sudo et al (1977) report left renal blood flows of 39.3 ± 2.6 ml/min at mean arterial blood pressures of 93 ± 4 mm Hg, in pentobarbital

anesthetized rabbits weighing about 3 kg. These researchers did not monitor blood and cardiovascular parameters, and make no mention of respiratory assistance to their animals. However, if cardiac output in a 3 kg rabbit is about 400 ml/min (Korner, 1963) and normal RBF is about one fifth of cardiac output, then each kidney might well receive about 40 ml/min. These flows are much greater than our calculated left renal blood flow of 13 ml/min. Adjusting our value according to an 80% PAH extraction (Sudo et al, 1977), still gives a very low effective RBF. Three factors may be responsible for differences between our urine production and clearance results, and those reported in the literature. First, halothane hypotension may have reduced arterial blood pressure below the lower limit for autoregulation. Second, our GFR and RBF calculations are based on clearance studies, but clearance studies may not be a reliable way of studying renal function under surgical conditions (Bálint, 1963). Third, anuria may be the rabbit's normal response to anesthesia and surgery.

In studies on anesthetized, fasted dogs, infusing an equivalent of 0.15 ml 0.9% saline per minute per 3 kg produced no significant variance in renal clearance studies from control values (Kövé, 1976). However, in a hypervolemic group under similar conditions, the sodium and water excretion was elevated greatly.

Of more than one hundred rabbits used in the development of this research, only one multiple renal vessel was seen. Korner (1963), Forster (1947) and Brod & Sirota (1949) have demonstrated that renal studies in the unanesthetized rabbit are reproducible

and that, in a non-distressed state, the rabbit's circulation is stable. Research by Blake and Jurf (1968), in rabbits weighing from 2-3 kg undergoing major abdominal surgery, suggests that 0.7 ml/min of a 0.5% saline solution containing potassium chloride and mannitol, is sufficient to induce a mild diuresis. Mannitol is a powerful osmotic diuretic, and can also prevent swelling of kidney tubular cells (Boba & Landmesser, 1961). A need for its use in the rabbit during surgery, further suggests that the rabbit is not a good model for renal research involving surgery.

SUMMARY AND CONCLUSIONS

Under the conditions of these experiments, fasting causes polydipsia and diuresis in rabbits. Fasted rabbits conserve electrolytes. Halothane can be used as sole anesthetic agent in rabbits, but causes significant hypotension. Fluid administration, of 0.5 ml of a 0.9% saline solution intravenously, is beneficial to rabbits weighing about 3 kg, during anesthesia and surgery. Saline infusions much less than or much in excess of this, are undesirable in metabolic studies on anesthetized rabbits. Excessive saline infusion leads to the production of abnormal urine, the reduction of heart rate and blood pressures, and the creation of acidosis, during surgery. Under the condition of optimal saline administration (0.5 ml/min/3 kg), halothane anesthetized rabbits do not reliably produce urine during a procedure involving surgery, and so are not a suitable model for such renal studies.

CHAPTER V

SURVEY OF THE LITERATURE

A. PURPOSE OF RENAL FUNCTION

The mammalian kidney is the seat of intense metabolic activity. It receives large volumes of blood flow and consumes a conspicuous amount of oxygen. For practical purposes, the kidney is the major mode of water loss and the only filter capable of retaining base and losing acid (Boba & Landmesser, 1961), although other tissues have some similar responses to changes in acid-base parameters (Crepeau et al, 1977).

B. INTRACORPOREAL FACTORS INFLUENCING RENAL FUNCTION

Renal Anatomy

The functional unit of the kidney, is the nephron. It consists of a glomerular capillary network that is surrounded by Bowman's capsule, a proximal convoluted tubule, a loop of Henle, a distal convoluted tubule, and a collecting duct.

In 1842, Bowman defined fundamental renal blood flow as being first through the glomeruli, then to the tubular and collecting areas, and out through the veins. This means that blood to the capillary beds around the tubules and nourishing the parenchyma, has first passed through the glomerular capillaries (Boba & Landmesser, 1961).

Trueta et al (1947) anatomically delineated two types of glomeruli: cortical (superficial) and juxtamedullary. The distinction between the two glomeruli was that a large calibre efferent blood vessel passed from the juxtamedullary glomerulus into the medulla, while the small calibre efferent blood vessel from the cortical glomerulus divided into a cortical capillary network. These are now considered distinguishing features of cortical and juxtamedullary nephrons, but it is recognized that some cortical type nephrons may be situated near the medulla and vice versa. Another difference between these types of nephrons is that juxtamedullary nephrons have a loop of Henle which extends well into the inner renal medulla; superficial cortical-type nephrons have a shorter loop of Henle which only extends into the outer medulla. Juxtamedullary nephrons are thought to have greater sodium reabsorptive capacity due to their longer loops of Henle (Blake & Jurf, 1968; McCombs & Berkowitz, 1976).

Apart from the loops of Henle, both nephron types are largely cortical, with the glomeruli, most of the proximal and distal tubules and the first portion of the collecting duct, within the cortex (Valtin, 1973).

• Studies with isotope-labelled microspheres demonstrate that almost all microspheres entering the kidney are trapped in the glomerular capillaries (Neutze et al, 1968; Sudo et al, 1977). The renal medulla was free of them. This is consistent with the view that medullary blood supply is usually post-glomerular. Therefore, oxygen supplied to the parenchyma has already passed

through the glomerulus.

Other important renal vascular features are that blood at the afferent glomerular vessel has a high pressure head and that this vessel has a greater bore than the efferent one (Boba & Landmesser, 1961). It can be seen, therefore that a high pressure gradient can easily be created within the glomerulus. This would facilitate filtration, if the glomerular walls remained at all permeable to blood serum components. If afferent arteriolar pressure is sufficiently low, filtration will cease, but flow to the renal parenchyma may not, so the parenchyma will not necessarily become anoxic.

Two other anatomical factors bear mentioning before proceeding. First, although the nephron is the functional unit of the kidney, it is of import that the nephrons, as a group, are encapsulated. This capsule is formed of strong fibrous tissue with little elasticity. The capsule will tolerate great increases in tension without significant expansion (Boba & Landmesser, 1961). Serious disturbances in renal physiology might be anticipated from acute elevations in intracapsular pressure. Decapsulation will prevent increases in renal vascular resistance after trauma or hemorrhage (Bounous et al, 1960) but this is not an innocuous procedure, as renal autoregulation is permanently abolished. Second, although the kidneys are thought of as being alike in every way, the left kidney is usually selected for study because of the length of its pedicle and because the liver does not interfere with its dissection (Neely & Turner, 1959).

Direct stimulation of the renal nerves can cause vasoconstriction. When it does, the blood remains in the systemic circulation. This is taken to indicate that the afferent vessel constricts (Boba & Landmesser, 1961). Under severe conditions of such vasoconstriction one would expect ultimate tubular damage, if it occurred, involving most structures in the cortex, but would damage be confined to the cortex?

In 1947, Trueta published studies showing that in the rabbit, the blood flow through the kidney might, on occasion, fail to perfuse the peripheral part of the renal cortex, while being maintained through the deepest zone of the cortex and through the medulla. The literature reports unpredictable and variable duplication of this 'cortical ischemia with juxtamedullary shunting' (Study & Shipley, 1950). By stimulating the anterior sigmoid gyri of the cerebral cortex, giving intra-arterial adrenaline, inducing acute hypotension, causing renal arterial spasm, stimulating the splanchnic nerves or the renal plexus, injecting a posterior pituitary extract intra-arterially to the kidney, or stimulating the proximal end of a divided sciatic nerve, many investigators have observed 'cortico-medullary shunting' not only in the rabbit, but in the cat, dog, monkey, and sheep (Goodwin et al, 1949; Frey, 1936, 1937; Spanner, 1938; Simkin et al, 1948; Trueta et al, 1947; Daniel et al, 1952; Jirka et al, 1961; Pilkington et al, 1965; Cort & Barron, 1948; Oliver et al, 1951; Sadler & Tuttle, 1963; and Wilson et al, 1971). Ash (1933) defines cortical ischemia with anuria as a clinical pathological

entity in humans. However, some of these investigators admit inconsistent results (Daniel et al, 1952). Another group of investigators (Reubi & Schroeder, 1949; Kahn et al, 1950; Houck, 1951; Study & Shipley, 1951; Aukland, 1967) using similar techniques, demonstrated patchy ischemia involving both cortex and medulla, but did not obtain evidence for cortex-to-medullary shunting of blood. Those favoring the possibility of a shunt generally concede that it occurs only under severely abnormal conditions. Some specify that when cortical ischemia occurs, circulation is maintained in the medulla and the juxtamedullary glomeruli. This more moderate approach seems to come closer to the truth than insistence that a state of totally aglomerular renal perfusion could continue for very long.

Since medullary blood flow is reliant on blood passing through the juxtamedullary glomeruli (at least) with their afferent and efferent arterioles, it is likely that medullary circulation is governed by these arterioles (von Möllendorff, 1930; Mitchell, 1950 a, b, 1951, and 1958; Aukland, 1967). However, it is not inconceivable that ischemic injury could cause extensive tubular damage and swelling and that this might cause a passive reduction in cortical flow.

Some facts are known about blood flow distribution within the kidney. From the multi-exponential disappearance of ^{85}Kr from the kidney, Thorburn et al (1963) concluded that outer cortical flow is normally faster than inner cortical and outer medullary flow, which is faster than inner medullary flow.

While it is possible, therefore, that anatomical arterio-venous anastomoses may exist (Isaacs, 1857; Ludwig, 1871; Gross, 1917; Gömöri, 1961), conditions under which they represent the main renal blood pathway are very rare (Daniel et al, 1952) if existent at all among mammals. It is likely, however, that the ratio of cortical to medullary blood flow can be decreased in all mammalian kidneys. Whether this demonstration of neurovascular control of renal circulation represents a shunt, or a progressive peripheral vasoconstriction of the renal vasculature, or a passive result of tubular swelling, has not been finally determined. It is known that there is more poorly-developed smooth muscle in the medullary vasa recta than that of the afferent or efferent glomerular vessel (von Möllendorff, 1930) and that there are relatively fewer medullary nerve fibers (Mitchell, 1950 a, b, 1951), than cortical ones.

Renal Physiology

Nervous Effects

Trueta (1947) suggested that the cortical-medullary blood flow distribution was under control of the nervous system. While anatomical studies indicate renal innervation of both sympathetic and parasympathetic origin (Mitchell, 1951; de Muylder, 1952; Stöhr, 1952), physiological studies indicate that nervous control of the kidney is predominantly sympathetic (Kaplan et al, 1953; Page & McCubbin, 1953; Yamagishi & Azuma, 1963; Concha & Norris, 1968). Sympathetic innervation originates from T₆ through L₃.

segments of the spinal cord inclusively. Parasympathetic innervation comes from the vagus. High frequency stimulation of the renal nerves always produces vasoconstriction (Study & Shipley, 1950; Houck, 1951b; Block et al, 1952; Boba & Landmesser, 1961; Concha & Norris, 1968). Low frequency stimulation is reported to have a variable effect on the vessels (Bradford, 1889; Concha & Norris, 1968). That high frequency stimulation produced afferent arteriolar constriction, is evidenced by a greater reduction in the GFR than in the RBF (Study & Shipley, 1950; Houck, 1951b; Shipley & Study, 1951). This increased afferent arteriolar resistance was concomitant with reductions in urine flow, and inulin and diodrast extraction (Houck, 1951b; Shipley & Study, 1951) and increases in oxygen extraction in dogs (Houck, 1951b). Block et al (1952) suggests that neurogenic renal vasoconstriction can not be kept severe, because of the adaptation phenomenon. He feels that maximal neurogenic vasoconstriction is probably a very brief emergency measure. Any sustained effects after neurogenic vasoconstriction may be due to humoral system mediation. It has been observed, for example, that splanchnic stimulation causes increased levels of catecholamines in the circulation (Goodwin et al, 1949). It has also been suggested that prolonged antidiuresis after continuous renal nerve stimulation, is mediated by increased antidiuretic hormone (ADH) in the circulation (Verney, 1946; Block et al, 1952).

Representing the sympathetic nervous system, both alpha and beta adrenergic receptors are believed to be present within the

renal vasculature (McCombs & Berkowitz, 1976). Loeffler et al (1972) suggests that while total renal blood flow is largely governed by alpha receptors, beta receptors mediate renin release.

Blockade of alpha receptors decreases arterial blood pressure. It also reduces renal vascular resistance and increases both cortical and total renal blood flow (McCombs & Berkowitz, 1976; Weber et al, 1976). As the RBF increases, there is a proportional increase in the GFR, and therefore a constancy of the filtration fraction (FF). This indicates a reduction in both afferent and efferent arteriolar tone. There is no consistent change in sodium or water excretion (Moyer et al, 1955; McCombs & Berkowitz, 1976). Alpha receptor blockade can also be used to reverse the effects of anoxia on the outer cortical flow (Weber et al, 1976), but will not overcome the effects of combined anoxia and warm ischemia.

Blockade of beta receptors produced a significant decrease in sodium excretion, in dogs, according to McCombs and Berkowitz (1976). They suggest that this may be due either to afferent glomerular arteriolar constriction or increased perfusion of juxtamedullary nephrons (with their longer loops of Henle). The former, certainly, may be mediated by renin release.

Renal nerves are not indispensable to the normal functioning of the kidney. Releasing the kidney from its nervous supply by denervation, results in an increased sodium, chloride, and water excretion in cats and rabbits (Blake & Jurf, 1968; Kunze et al,

1977). This may be mediated by intrarenal humoral inhibition of tubular reabsorption, or by a redistribution of glomerular filtration with enhanced perfusion of the outer cortical nephrons (Blake & Jurf, 1968).

Humoral and Electrolyte Effects

In 1950, Berne and Levy experimentally reduced canine cardiac output by pulmonary artery constriction. This reduced GFR, RBF, urine output and sodium excretion. These results were not changed by renal denervation, so they were considered a result of humoral elements causing vasoconstriction (Papper & Ngai, 1956). This was also concluded by Mokotoff and his co-workers (1948).

Both epinephrine and norepinephrine produce marked renal vasoconstriction and increase renal vascular resistance (Blake, 1955; Papper & Ngai, 1956; Aukland, 1967). This always reduces the RBF (Blake; Papper & Ngai; Aukland; Houck, 1951a) but may or may not reduce the GFR (Blake; Papper & Ngai; Houck). If these catecholamines affected both the afferent and efferent glomerular arterioles, equally, then the GFR would decrease with the RBF. If it predominantly affected the efferent arterioles, then the GFR might not change with the reduced RBF. The variable results indicate uncertainty as to the predominantly affected renal vessels (Blake, 1955). In either case, catecholamine-induced vasoconstriction is partly responsible for the pronounced renal effects of shock, sepsis, or low (hypoxic) perfusion states (Weber et al, 1976).

In contrast to catecholamine-induced renal vasoconstriction, prostaglandins, which are produced by the kidneys, are thought to cause renal vasodilation (Dunn & Howe, 1977) with increased renal blood flow and natriuresis.

In addition to hormones with mainly vasoactive effects, there are those with much more specific actions. Antidiuretic hormone (ADH), of posterior pituitary origin, increases the water permeability of the distal tubules and collecting ducts, and thereby allows increased water reabsorption (Papper & Ngai, 1956; Boba & Landmesser, 1961; Valtin, 1973). There is evidence that adrenal medullary hormones (catecholamines) may produce sustained anti-diuresis by stimulating ADH release (Papper & Ngai, 1956).

Finally, sodium balance is singled out for special maintenance. It is regulated through the renin-angiotensin system of hormones mediating the adreno-cortical release of aldosterone (Boba & Landmesser, 1961). Aldosterone increases the renal tubular reabsorption of sodium (Valtin, 1973). Furosemide, an exogenous pharmaceutical, has an opposite effect (Naber & Madsen, 1973). Serum sodium levels are apparently very important. When they decrease, a diuresis occurs (Kunze et al, 1977). The mechanism is not certain, but it is known that an extracellular sodium reduction of as little as 5% will increase arterial blood pressure (Kunze et al, 1977). This increased blood pressure (mediated by the carotid sinus baroreceptors) may be the reason for the diuresis (Blake, 1955; Kunze et al, 1977). There is some evidence for preferential perfusion of nephrons with high or low

sodium reabsorptive capacity, depending on the state of sodium balance (McCombs & Berkowitz, 1976).

Autoregulation

The pressure required to initiate blood flow through the renal vascular bed is from 7 - 14 mm Hg (Selkurt, 1946b; Shipley & Study, 1951). At such low pressures, there is no filtration. Urine flow begins at a mean arterial pressure of about 60 mm Hg and increases, with increasing renal arterial blood pressure, until at very high perfusion pressures (greater than 300 mm Hg) it can be as high as 75% of the GFR (Shipley & Study, 1951). However, over a wide range of arterial pressures the RBF, GFR, and FF remain essentially constant (Berne & Levy, 1950; Forster, 1947; Forster & Maes, 1947; Shipley & Study, 1951) in dogs. This is termed autoregulation. The upper and lower limits have been defined as 180-200 and 70-80 mm Hg respectively (Selkurt, 1946b; Shipley & Study, 1951; Rothe et al, 1971; Leighton et al, 1977). Leighton et al (1977) has observed that during sodium nitroprusside-induced hypotension in dogs, autoregulation is operative at 50 mm Hg.

Despite the occasional contrary view (Osbaldiston & Fuhrman, 1970), renal nerves are generally considered unnecessary for autoregulation (Quinby, 1916; Maluf, 1943; Selkurt, 1946b; Shipley & Study, 1950; Boba & Landmesser, 1961; Leighton et al, 1973). This view is supported by renal transplant work in most species (Murray et al, 1958, for example) of experimental animal and man. In vivo there are circumstances which exert renal blood flow

control despite a mean arterial blood pressure greater than the lower limit for normal autoregulation. Hemorrhage, acute hypoxia or placing one foot in ice water (Talso et al, 1948) are examples of such circumstances. In the absence of over-riding mechanisms both the GFR and total RBF are subject to autoregulation. Thureau (1964) and most others consider cortical blood flow to be autoregulated. Grangsjö and Wolgast (1972) show evidence that medullary blood flow is also autoregulated, at least in dogs.

There are several theories to explain autoregulation. Bayliss (1902) proposed a myogenic hypothesis, that vascular muscle responds to a stretching force by contraction and to a reduction in this force, by relaxation. A metabolic hypothesis suggests that the accumulations of lactic acid, carbon dioxide, and other metabolites during decreased blood flow, may cause vasodilation (Berne, 1964). A tissue pressure hypothesis proposes that perivascular pressure is elevated by the perfusion pressure-related extravasation of fluid from the capillaries (Westermarck & Wahlin, 1969). Thureau and Levine (1971) claim that a juxtamedullary apparatus at the macula densa can sense sodium concentration within the ascending limb of the loop of Henle. This may cause events which release angiotensin II. The latter agent would then act on the afferent glomerular arteriole, which would constrict and reduce the GFR. Studies of renal perfusion with mineral oil at varying pressures, have demonstrated autoregulation and suggest that the Thureau/Levine suggestion is not the unique answer (Leighton, 1973). Honda et al (1972) suggest a

common underlying mechanism between postocclusive reactive hyperemia and circulatory autoregulation. Their studies suggest that diminished tissue pressure is not a primary cause of autoregulation, but that some myogenic and metabolic factors may be jointly responsible.

Blood Flow

Lingårdh (1972) found that blood flow to the left kidney of healthy humans was slightly (10%) higher than that to the right kidney. Others (Neutze et al, 1968) have shown tissue flows to the right and left kidneys that are almost identical, in the rabbit. These results are not necessarily contradictory. Within a given kidney, the blood flow is greatest in the outer cortex and decreases toward the inner medulla (Sudo et al, 1977; Thorburn et al, 1963). While the flow to the medulla is as low as seven percent (Leighton et al, 1973) in the dog, this flow may have a tremendous effect on interstitial osmolarity in the area of the collecting ducts and loops of Henle. Medullary flow can, thereby, greatly influence urinary composition.

One blood flow factor bears re-mentioning: if a sufficiently low afferent arteriolar pressure to the glomerulus is reached, filtration will cease, but flow to the parenchyma may not. Because of this fact, some cases of hypotension do not constitute totally anoxic conditions within the parenchyma (Boba & Landmesser, 1961). This permits recovery of renal function after a certain amount of hypotension.

Indirect Measurements of Renal Function

The fraction of the RBF which is filtered through the glomeruli, is called the filtration fraction (FF). Osbaldiston and Fuhrman (1970) found an average filtration fraction in resting cats, of 0.21. This figure corresponds to that for the resting dog, but is much greater, they claim, than that reported by Brod and Sirota (1949) for the resting rabbit. In fact, the average filtration fraction from the results of the work by these latter researchers, was identical (0.21). Stedman's Medical Dictionary (1972) reports that an average filtration fraction for the human kidney is about 0.22. It is likely that this value for the filtration fraction of most mammals, is normally quite accurate.

Methods for determining the RBF and GFR are quite varied. Renal blood flow is either directly (flow meter, rotameter, or thermodilution -- White et al, 1967) or indirectly measured, while the GFR is only indirectly measured. Methods for measuring the GFR are based on the urine flow rate and relative blood and urine concentrations of a substance that is filtered at the glomerulus, but neither secreted nor reabsorbed from the tubules. Inulin is considered such a substance.

Bull and Metaxas (1962) found that in normal renal function, cleared substances are insignificantly removed in the lymph, so the indirect methods of measuring renal parameters, were considered generally reliable. Since inulin concentration determinations were time consuming and since radioactive labelled inulin is rather expensive, other labelled substances were tried (for

example, $^{51}\text{Cr-EDTA}$ -- Stacy & Thorburn, 1966; Lingårdh, 1971), with questionable success (Lingårdh, 1972). Results with each new compound, are compared to those obtained with inulin. Young et al (1969) demonstrated that some $^{51}\text{Cr-EDTA}$ is reabsorbed in the tubules.

Indirect determinations of the renal blood flow have taken a similar route. Methodology in this case is based on the urine flow rate and relative blood and urine concentrations of a substance that is completely extracted (by secretion and filtration without any reabsorption) from all blood flowing through the organ. Para-aminohippurate (PAH) is most commonly used. There is from 87 to 96 percent extraction of PAH from renal blood (Selkurt, 1946a; Phillips & Hamilton, 1948; Korner, 1963). PAH clearance is usually considered about 85-90% of the RBF (Valtin, 1973). Because PAH is mainly secreted by proximal tubules in the renal cortex, the ratio of PAH clearance to actual RBF is considered by some, an estimate of the ratio of cortical to total renal plasma flow (Lindeman & Papper, 1975). To distinguish actual renal plasma flow from that determined by indirect or functional methods, the concept of an effective renal plasma flow (ERPF) is used (Smith, 1937).

Some substances have been substituted for PAH (Lingårdh, 1971, 1972). Iodinated hippuran ($^{125}\text{I-}$ or $^{131}\text{I-}$) is an example. However, because of strong binding of some of the I-hippuran to plasma protein, it can not all be excreted by the kidney (Lingårdh).

There are problems associated with these traditional indirect methods of assessing renal function according to clearances. Anuria makes the methods useless. Research in poisoned frogs demonstrated that the tubular walls under these conditions can permit unselective diffusion of the entire filtrate back into the circulation (Phillips & Hamilton, 1948). Others have demonstrated that under conditions such as ischemia, shock, reduced perfusion pressures, renal nerve stimulation, tubular damage, or oliguria, clearance techniques are unreliable ways of estimating RBF or GFR (Lucké, 1946; Selkurt, 1946a; Goodwin et al, 1949; Study & Shipley, 1950; Habif et al, 1951; Block et al, 1952; Bálint & Forgács, 1960; Boba & Landmesser, 1961; Jirka et al, 1961; Bálint, 1963; Wilson et al, 1971; Sudo et al, 1977).

Specific Ureteral Influence

Wharton (1932) demonstrated intricate sympathetic pathways between the kidneys and the ureters. In the animal lab, it is common knowledge that rough ureteral handling produces anuria (Goodwin et al, 1949). This may be due to ureteral constriction (spasm), because it would raise the ureteral pressure. Such an elevation in pressure to 50 mm Hg or more, will greatly impair autoregulation (Rothe et al, 1971). In fact, Malvin et al (1964) suggests that an increasing number of nephrons will stop filtering completely, if the ureteral pressure exceeds one third of the mean arterial blood pressure.

Experimental work shows that following ureteral occlusion there is an immediate increase in ipsilateral RBF (Vaughan et

al, 1971; Naber & Madsen, 1973) and an associated fall in renal resistance. This transient vasodilation was followed by a gradually increasing resistance, with a markedly decreasing renal blood flow (Levy et al, 1937; Vaughan et al, 1971; Naber & Madsen, 1973). The glomerular filtration rate falls but occasionally not as rapidly as the RBF (Naber & Madsen). This is perhaps due to renin release and increased efferent arteriolar tone (Naber & Madsen). This total response to ureteral occlusion is interpreted as a reduced filtration rate per nephron, due to elevated back pressure. The response is not changed by denervation, adrenergic blockade, renin depletion, or contralateral nephrectomy (Vaughan et al, 1971). High sodium and water reabsorption accompany ureteral occlusion or partial ureteral obstruction (Naber & Madsen, 1973). During ureteral occlusion there is some pyelolymphatic flow of urine via the hilar lymph, but most of any urine formed becomes pyelovenous backflow (Naber & Madsen, 1973).

Specific Hypoxic or Ischemic Effects

The very title of this section may be inappropriate because traditionally the 'specific effects of ischemia' are not separated from the potential detrimental effects of such factors as extended anesthesia, handling and reopening of the peritoneum. In addition, experimenters are not unanimous in their ischemia model-systems. They may occlude the renal artery, the renal vein, the renal pedicle, the pre-renal aorta, or both the pre-renal aorta and the renal artery. When one renal artery is occluded, in dogs or rabbits, there is upon release of occlusion, some loss

of renal function (Scarff & Keele, 1943; Selkurt, 1946a; Van Slyke, 1948; Kahn et al, 1950; Moyer et al, 1957; Leary et al, 1963). The functional impairment is proportional to the duration of clamping: 3 hours of clamping, or more, seems to create irreversible damage. When the pre-renal aorta is also clamped in dogs, the damage in shorter clamping times, is more severe (Moyer et al, 1957). When only the pre-renal aorta is clamped, although the mean arterial blood pressure on the distal side drops to below 30 mm Hg (the irreversible shock level) and no urine is produced, there seems sufficient pressure to prevent post-occlusive renal damage even after 3 hours (Moyer).

Continuous occlusion of the renal artery for 2 hours may be tolerated, but 2 hours of intermittent occlusion (3 minutes of flow every 30 minutes) is very damaging (Leary et al, 1963; Stueber et al, 1959; Yoho et al, 1960) to the canine kidney. According to Neely and Turner (1959) venous clamping per unit time may be more damaging to canine kidneys than arterial clamping. This, they suggest, is due to the Crowell-Webb theory concerning the detrimental effects of formed elements on the static circulation. Wilson et al (1971) believes the difference to be due to repetitive intra-renal trapping of vasoconstrictive elements, a similar hypothesis. Porch et al (1959) specify that the capsular vessels do not provide any protection against the effects of vascular occlusion and that venous occlusion alone is no worse than arterial occlusion alone. Obviously, this is still contested.



Selkurt (1946b) has observed that brief renal ischemia causes the appearance of renin in canine renal veins. This suggests to him that the ischemic kidney is the site of production of pressor substances or their precursors. Honda et al (1968) ascribe post-occlusive reactive hyperemia in the rabbit kidney to liberation of vasodilator substances from the ischemic tissues, but this, they claim, is only a transitory response and is followed by vasoconstriction.

Moderate systemic anoxia, increased pCO_2 and reduced pH of perfusion blood, produce renal vasodilation as well, and this can increase RBF, GFR and urine output (Papper & Ngai, 1956; Honda et al, 1972). The latter may be due to a brief impairment of the tubular reabsorptive processes.

Boba & Landmesser (1961) summarize well the potential effects of ischemia. They suggest that inadequate RBF causes hypoxia and that eventually cellular damage will result. Damaged cells will tend to absorb water and swell. Because of the inelasticity of the renal capsule, high pressures can be created and may cause tubular collapse. They add that the administration of a powerful osmotic diuretic will both restore urine flow and prevent cellular swelling and tubular dysfunction. With regard to ischemia, they have demonstrated that while the effects of 2 hours of hypoxia may not be seen with conventional histology, abnormal enzyme patterns and total disruption of some oxygen-carrying enzyme systems can be seen much earlier.

Acute Renal Failure

Acute renal failure is characterized by decreasing urine output (progressive oliguria), rising serum creatinine and potassium levels, diminished clearances, reduced urine osmolarity, and altered intrarenal hemodynamics (Sudo et al, 1977). This failure frequently follows hemorrhage, burns, dehydration, trauma, incompatible blood transfusions or peripheral circulatory failure (Moyer et al, 1955). Suggested causes of acute renal failure include: exposing a damaging compound to the tubules, mechanically blocking the tubules with, for example, hemoglobin or myoglobin, or the interruption of the tubular blood flow or oxygen supply (Moyer et al, 1957; Boba & Landmesser, 1961). Many investigators have found that the tubular cells are particularly damaged by hypoxia (Mallory, 1947; Trueta et al, 1947; Oliver et al, 1951; Moyer et al, 1957; Sudo et al, 1977).

Mechanisms to account for the development of oliguria in renal failure include: reduced GFR due to vasoconstriction and reduced RBF, or decreased glomerular permeability; back-leakage of filtrate across a damaged tubular epithelium; or mechanical blockage of the tubules (Bank et al, 1967; Steinhausen et al, 1969; Wilson et al, 1971; Blantz, 1975; Stein et al, 1975; Sudo et al, 1977). Sudo et al (1977), from their studies in the rabbit, claim that back-diffusion of the filtrate across a damaged tubular epithelium, is the major cause. They demonstrated that zonal blood flow during oliguria is re-distributed from the cortex toward the medulla, but that this re-distribution was poorly

correlated with the decrease in urine output. This indicates that cortical blood flow is reduced due to swelling and damage rather than being the result of an over-riding shunt mechanism.

C. EXTRACORPOREAL FACTORS INFLUENCING RENAL FUNCTION

Cannulations and Catheterization

It is theoretically possible that cannulations or catheterization of blood vessels, per se, might influence renal function. Arterial spasm is often caused by stimulation of the inside of the vessel wall, particularly in the smaller arteries (Göthlin & Olin, 1970). Puncture of the femoral artery with trauma to the femoral nerve, is said to consistently cause arterial contraction. Catheterization or cannulation of renal arteries or veins, is usually associated with only brief changes in renal function, to a very slight degree (Selkurt, 1946a; Lindell & Olin, 1957; Korner, 1963; Bodforss et al, 1964; Leiter, 1965). The injection of contrast media into the renal artery is not entirely innocuous, however, and some damage may occur, contingent upon the type and dose of the medium and its application time (Bodforss et al, 1964; Leiter, 1965).

Surgery and Anesthesia

General Effects of Anesthesia and Operation

General anesthesia is known to depress myocardial function and usually cardiac output (Berne & Levy, 1950; Neutze et al, 1968). The posture of the operated patient, can also influence

cardiac output, by altering the venous return to the heart (McIntyre, 1971). Intraoperative bradycardia is often caused by vagal stimulation, but this can be overcome with atropine, in many cases (McIntyre, 1971). During general anesthesia there are often changes in tissue metabolism and catecholamine output, with complex effects on neurogenic vasomotor control (Neutze et al, 1968).

Operation and trauma induce some cellular and tissue breakdown. This releases large amounts of potassium and protein (Boba & Landmesser, 1961). To re-establish osmotic equilibrium and prevent further damage, three steps are essential: potassium ions must be removed from the area and diluted throughout the body water; water must move into the area in order for osmotic pressure to be re-established; and, sodium must diffuse into the area in order for isoionicity to be re-established. These processes are referred to as the 'third space' concept and are widely accepted (Boba & Landmesser, 1961). This redistribution of body fluids and sequestration of sodium creates a need for sodium conservation. This may be partly responsible for temporary disturbances in renal function.

The suppression of renal function by general anesthesia alone, was first described by Pringle in 1905. All general anesthetics significantly diminish RBF, GFR, and water and electrolyte excretion if there is sufficient depth of anesthesia (Habif et al, 1951; Glauser & Selkurt, 1952; Papper & Ngai, 1956; Boba & Landmesser, 1961; Kapur et al, 1972). This change in the absence

of significant drops in arterial blood pressure, indicates the over-riding of autoregulation.

Blake and Jurf (1968) report that surgery, anesthesia, and most other experimental procedures have an equal effect on both kidneys. They report that direct handling of one kidney is an exception, and that the handled kidney of the rabbit may display impairment of renal function for up to one hour, relative to the unhandled kidney.

Promptly after injury or surgery, kidney mechanisms are set in play to retain water and sodium (Moyer, 1950; Boba & Landmesser, 1961). While many believe that this retention is independent of need, Boba and Landmesser (1961) do not. They claim that these mechanisms will only result in oliguria or anuria if sodium and water are withheld. The intrinsic system is not without draw-backs, however, because Moyer (1950) has observed that, in dogs, the reduction in the rate of excreting chloride ions is greater than the reduction in the rate of excreting sodium. This leads to excessive chloride levels. This post-operative oliguria with sodium, chloride, and water retention is commonplace (Moyer, 1950; Habif et al, 1951; LeQuessne & Lewis, 1953; Dudley et al, 1954; Kapur et al, 1972). Neither large amounts of sodium nor large quantities of fluid will relieve the situation once it occurs.

Renal function decreases, and renal sensitivity to surgery increases, with age (Kapur et al, 1972). A far greater determinant of renal sensitivity to surgery, however, is the type of

operative procedure. Intra-abdominal operations with ureteral disturbance, packs on the kidneys, and intestinal and mesenteric handling, are followed by highly significant depressions of RBF and GFR (Moyer, 1950; Kapur et al, 1972). Again, this may well be due to catecholamine release (Goodwin et al, 1949). The anesthetic agent per se is usually implicated only during the actual period of anesthesia (Moyer, 1950).

Effects of Specific Anesthetics

1. Spinal anesthesia

During spinal anesthesia, Smith et al (1939) found no alteration in renal hemodynamics. However, Corcoran et al (1947, 1948), Neumann et al (1945), Sancetta et al (1952), and Lynn et al (1952) report vasodilation of the anesthetized area and an altered RBF when the kidneys were within that area. Renal effects with spinal anesthesia are considered especially dependent on hypotension and reduced cardiac output (Papper & Ngai, 1956). These factors seem mainly to occur when vasodilation is so profuse that there is insufficient area for compensatory vasoconstriction (Papper & Ngai, 1956).

2. Premedications

Morphine or meperidine both reduce urine flow (Habif et al, 1951; Papper & Ngai, 1956). They are associated with an increased urinary electrolyte concentration, but total electrolyte output is also reduced. Morphine is considered by certain authors, to stimulate the release of ADH (de Boda & Sweet, 1938, 1940, and 1944). Handley and Keller (1950) claim that morphine

inhibits diuresis even in animals with diabetes insipidus, by reducing the number of functioning nephrons.

The additive effects of two or more drugs has only begun to be explored, and the effects of variable doses of concerted drugs may vary greatly even within a given species.

3. Alcohol

strauss et al (1950), Rubini et al (1955) and Kleeman et al (1955) have all demonstrated that ethyl alcohol causes a marked diuresis with a loss of water far in excess of that of electrolytes, and a resulting hypertonicity of the plasma. Kleeman believes this to be due to direct inhibition of ADH release. Clinical use of alcohol anesthesia is very limited.

4. Cyclopropane and ether

Even in light anesthesia with cyclopropane or ether, there is a redistribution of blood flow due to vasodilation in the skin and muscle, with vasoconstriction in the renal and splanchnic vascular beds (Papper & Ngai, 1956). In deep anesthesia with these agents, total peripheral resistance increases greatly and there is reduced blood flow to the skin, muscle, splanchnic and renal vascular beds (Papper & Ngai). Elliot (1912) and Brewster et al (1952) both demonstrated that ether anesthesia causes an increase in circulating catecholamines, which results in an increased cardiac output, hyperglycemia, and lactic acid accumulation in the plasma. Elmes and Jefferson (1942) showed a similar effect by ether or cyclopropane. Anesthesia with either agent invariably causes a reduction in RBF, GFR and water and

electrolyte excretion (Pringle et al, 1905; Stewart & Rourke, 1938; Moyer, 1950; Habib et al, 1951), not due to a water deficit. Papper and Ngai (1956) ascribe cyclopropane effects to either a stimulation of ADH release or increased activity of the adrenal medulla, or both.

5. Barbiturates

Barbiturate anesthesia has two serious disadvantages: an overdose is easily given, and it can seriously depress respiration (Murdock, 1969). In addition, barbiturates are known to influence renal hemodynamics (Leighton et al, 1977). They tend to reduce cardiac output (Berne & Levy, 1950), increase systemic blood pressure (Glauser & Selkurt, 1952), and decrease the ERBF, without greatly reducing the GFR. Glauser and Selkurt (1952) suggest that barbiturates narcotize the tubular cells of the kidney, and impair their function. Certain barbiturates are implicated in extensive retention of sodium and chloride (Habib et al, 1951; Papper & Ngai, 1956).

6. Halothane

During halothane anesthesia there is both a decreased heart rate and a diminished stroke volume (Westermarck & Wahlin, 1969). There is, therefore, a depressed cardiac output. Halothane also depresses reflex vasoconstriction without altering reflex vasodilation and reduces the vasoconstrictive response to norepinephrine (Cristoforo & Brody, 1968). This implies that there will be a reduced total peripheral vascular resistance. Halothane has been observed (Westermarck & Wahlin, 1969) to reduce renal

vascular flow resistance to 72% of control, in cats. The lowered cardiac output is considered (Westermarck & Wahlin, 1969) a more important cause of halothane hypotension, than the reduction in total peripheral vascular resistance.

Clearance studies, in cats, indicate a moderate reduction in the renal blood flow following exposure to halothane (Westermarck & Wahlin). This reduction is probably directly related to the induced hypotension.

7. Methoxyflurane

Methoxyflurane has been shown to reduce GFR, RBF and water and electrolyte excretion (McIntyre & Russell, 1971). It has been implicated in the depression of at least one renal enzyme system (McIntyre & Russell). Post-operative methoxyflurane effects have been debated. Taves et al (1970) first suggested that methoxyflurane metabolism could lead to the production of two known nephrotoxic agents: inorganic fluoride and oxalic acid. Mazze et al (1971 a, b) has suggested that the degree of post-methoxyflurane renal dysfunction is related to serum inorganic fluoride levels and urinary oxalate excretion. This anesthetic agent is not invariably nephrotoxic (Gillies, 1971; McIntyre & Russell, 1971; Hetrick et al, 1973). Gillies (1971) proposes that serum inorganic fluoride levels of below 50 $\mu\text{mol/l}$ are not likely to be associated with post-operative renal dysfunction. Thureau has shown that sodium concentration in the distal tubules rises when the GFR is zero. It is therefore possible that toxic levels of solutes may be present within the renal tubules during

low flow states, in spite of low serum levels of those solutes (Leighton et al, 1973). High serum levels of inorganic fluoride are, by contrast, often associated with high-output renal failure (Mazze et al, 1971a, b). Hetrick et al (1973) proposed that fluoride ions inhibit in a dose related way, the effect of ADH. Methoxyflurane anesthesia may also obliterate autoregulation, leaving the renal blood flow to rise or fall, *pari passu*, with arterial blood pressure, according to Leighton (1973).

D. THE RABBIT IN SURGICAL EXPERIMENTATION

The rabbit stomach empties slowly, and may still contain food after food deprivations of as long as five days (Murdock, 1969). For this reason, a fasted rabbit may still have a full stomach at surgery.

Rabbits are one of the most difficult and unpredictable species of laboratory animal, to anesthetize (Murdock). Pre-operative animal health is a significant factor in the rabbit reaction to anesthesia. Because of the expensive equipment and technical skill required, gaseous anesthetics are seldom used in the rabbit (Murdock). This animal is almost impossible to intubate through the oral cavity. They invariably hold their breath as long as possible at the first smell of ether; then, they usually inspire deeply, which may permit such high ether concentrations in the myocardial blood that the heart will stop (Murdock). Resuscitation efforts usually fail.

Murdock reports that anesthetic depth is difficult to assess

in the rabbit because they commonly close their eyes and the pupil is slow to react. He claims that squeezing between the toes of a foot provides a fairly reliable index of the surgical plane or third stage of anesthesia.

The rabbit has other interesting characteristics. Rabbits have an extremely high blood flow to the spleen (Neutze et al, 1968). They are coprophagic. It is possible for the urine flow to vary as much as 16-fold during water diuresis in non-excited rabbits, without changes in the GFR (Brod & Sirota, 1949). This 'normal urine flow' is believed to be dependent on tubular reabsorption of water, as with other mammals (Brod & Sirota). Some PAH apparently enters canine red blood cells both in vivo and in vitro, but not those of man nor the rabbit (Korner, 1963). Another dissimilarity between the dog and the rabbit is that in the latter, cortical nephrons with their short loops of Henle, account for about half of all nephrons, while in the former, the fraction is much less (Blake & Jurf, 1968). Finally, rabbits are extremely resistant to demonstrating histamine effects (Murdock, 1969) and rapidly metabolize atropine (Godeaux & Tønnesen, 1949).

A rabbit's right renal artery has a slightly cranial course, while its left renal artery runs more transversely (Adams et al, 1965). The traditional left-over-right choice for renal studies has been extended to the rabbit. The cardiac output of an unanesthetized rabbit weighing about 3 kg, is from 400-600 ml/min (Korner, 1963; and White et al, 1967, respectively). Its left

RBF is from 40-80 ml/min, accordingly (Korner, 1963; White et al, 1967; Neutze et al, 1968; Sudo et al, 1977). The GFR and RBF are only slightly higher in denervated kidneys, suggesting that the resting sympathetic constrictor tone of the rabbit renal circulation, is low (Korner). Sudo et al (1977) have reported a mean arterial blood pressure in the pentobarbital-anesthetized 3 kg rabbit, of about 93 mm Hg, a PAH extraction of about 79%, and a creatinine clearance of about 4 ml/min.

The spontaneous urine flow of the rabbit is reported as 0.05 to 0.2 ml/min (Korner, 1963). Some experimenters have desired more urine for clearance determinations and so give water by stomach tube (Houck, 1951b) or fluid intravenously. To augment the normal urine flow Korner (1963) gave 0.5 ml/min of a Ringer-Locke solution containing 5% mannitol to rabbits weighing from 1.5 to 3.5 kg. He found some blood volume expansion resulting in slight hemodilution. To replace loss of fluid, Sudo et al (1977) gave rabbits weighing about 3 kg, 1.2 ml/min of an isotonic saline solution. Their renal hemodynamic studies involved a midline abdominal incision. Other fluid administrations during renal studies involved: intravenous administration of 0.9% saline to a total volume of about 10 ml/kg (Kunze et al, 1977); intravenous replacement of the urine volume with 0.45% saline by McCombs & Berkowitz (1976); intravenous infusion of 100 ml/hr of 0.9% saline to dogs weighing 10-16 kg (Study & Shipley, 1950); and 0.85% saline at 2.5 ml/min to dogs weighing about 25 kg (Rothe et al, 1971). These all represent quite moderate fluid

fluid administrations.

Kaplan and Smith (1935), Dicker and Heller (1945, 1950), and Forster (1947) have observed an increase in GFR, RBF and glucose maximum tubular reabsorption rate, with a urine flow increasing proportionately to the GFR, after giving rabbits approximately 40 ml/kg of water by stomach tube. This has been interpreted (Brewer, 1977) as indicating the recruitment of previously unperfused glomeruli. This interpretation had been challenged, previously, in a study by Brod & Sirota (1949). The latter researchers' investigation was prompted by the difficulty involved in producing water diuresis in certain rabbits. They report that in the absence of renal ischemia, reflexly induced by excitation, urine flow appears to be independent of GFR in the rabbit, as with man and the dog. They further suggest that the excitement due to administering large amounts of water to rabbits, by stomach tube, is not unequal to other severe emotional disturbances. Brod and Sirota created such disturbances by shocks, banging noises, pinching, and tying rabbits to a retaining board. They demonstrated a resultant decrease in RBF that was not due to a decrease in systemic blood pressure and oliguria that was primarily due to a depressed GFR and RBF. This fright/pain reaction has been documented by others (Wolf, 1945; Goodwin et al, 1949; Berne & Levy, 1950), in other mammals including the human. Haterius (1940) attributes it to an increased secretion of ADH, but Brod and Sirota do not concur. They do report, however, that adrenalin in large doses mimics the reaction

and they stipulate that during its course, convulsions and death are not uncommon.

One final contribution by Brod and Sirota, is that the supine position, per se, does not seem to influence renal function. This is apparently supported by Forster and Maes (1947).

Korner (1963) concludes that while it is possible that rabbits respond differently to large water loads (two to three times their blood volume) than do other mammals, the possibility does not apply to moderate water loads. He is content that the unanesthetized resting rabbit is a satisfactory animal for studying renal circulation, but he warns against handling, restraining, or overhydrating these animals.

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